# Enteric Dysmotility

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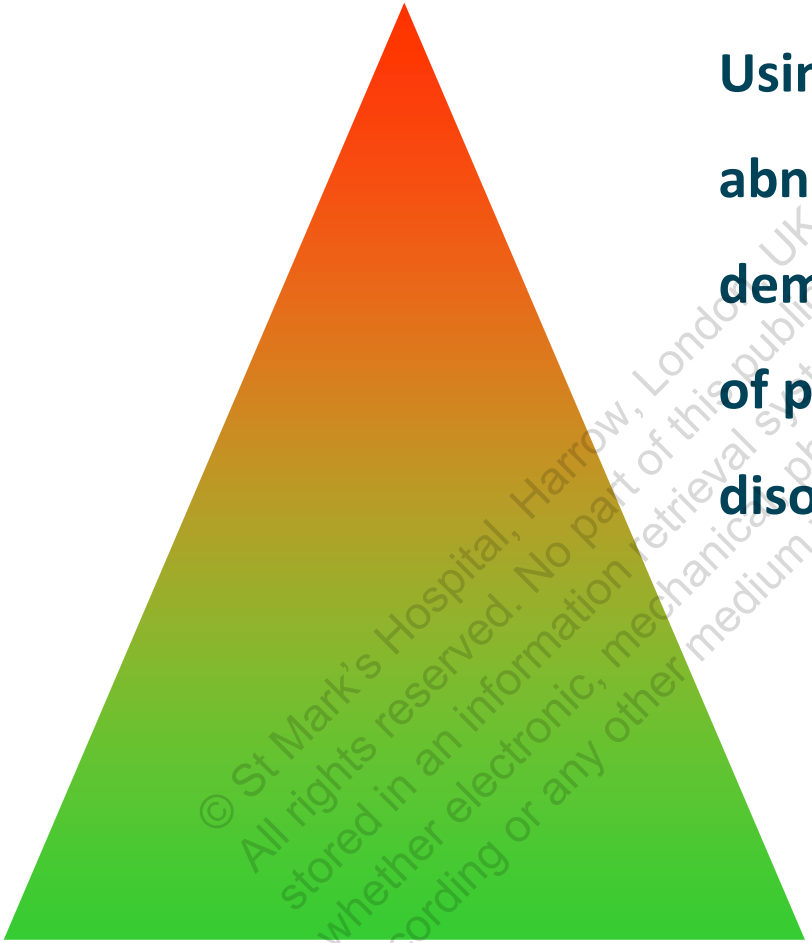
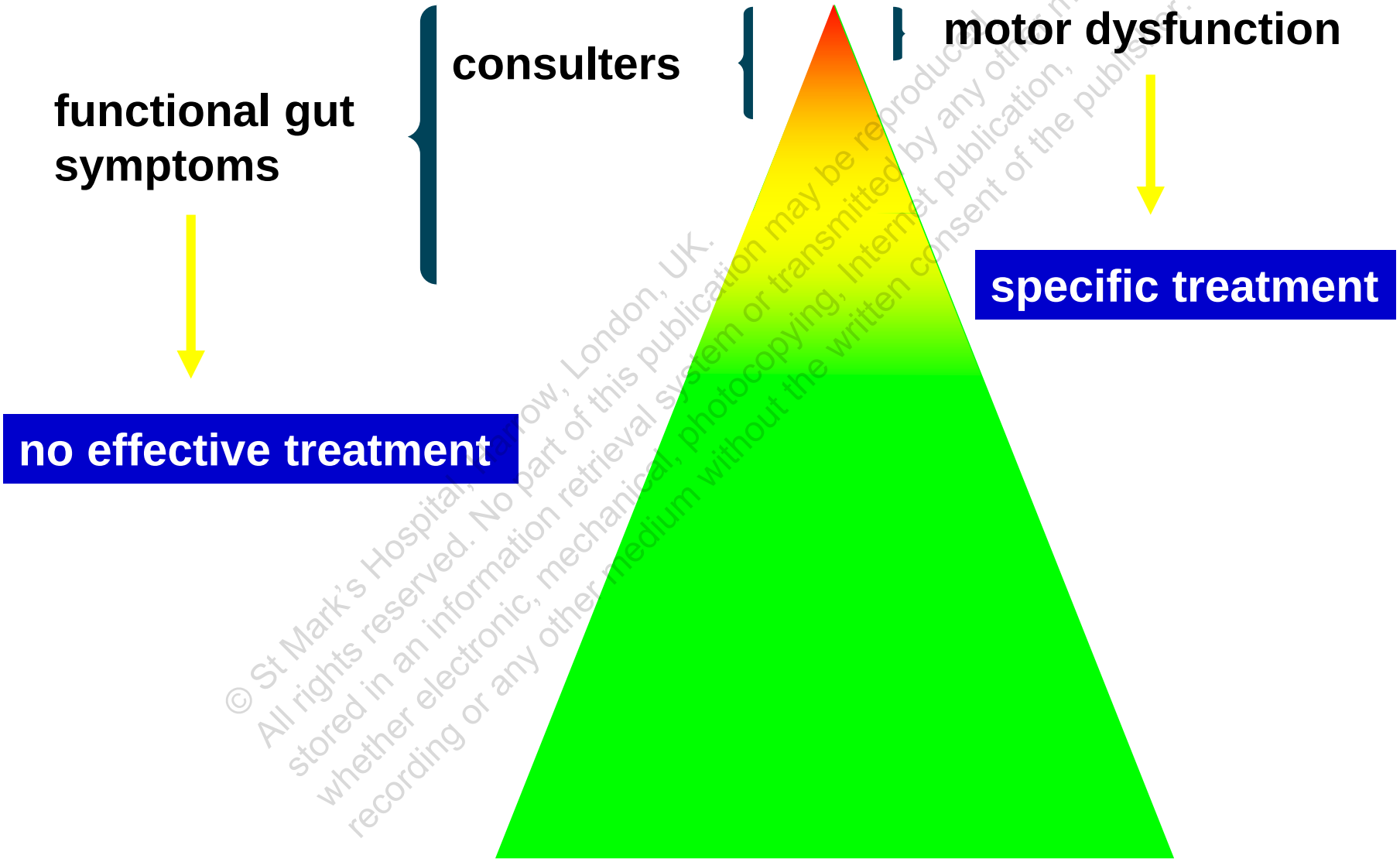
# Intestinal motility disorders



**Using different methodologies, abnormal intestinal motility can be demonstrated in a significant proportion of patients with functional intestinal disorders.**

# Intestinal motility evaluation



**Miss X**
**born 1965, nurse**

Type I diabetes since age 22

Diarrhoea and vomiting 3 years - unrelated to blood sugars
No evidence autonomic neuropathy

Euglycaemic clamp:
no effect

# Type I Diabetes and Coeliac Disease

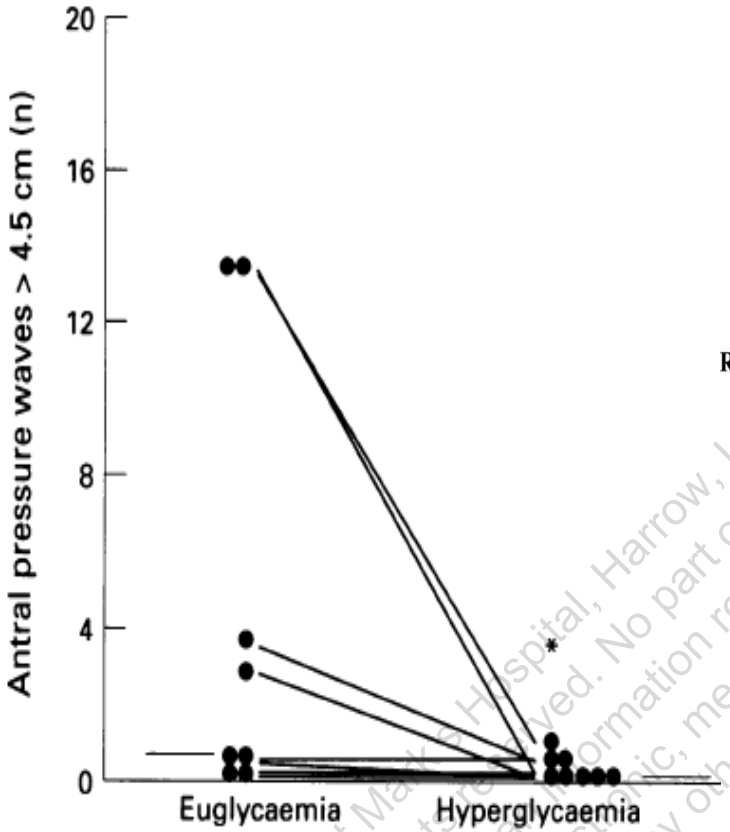
Prevalence Coeliac in type I DM ~ 5% (Cronin et al, Am J Gastro 1997)

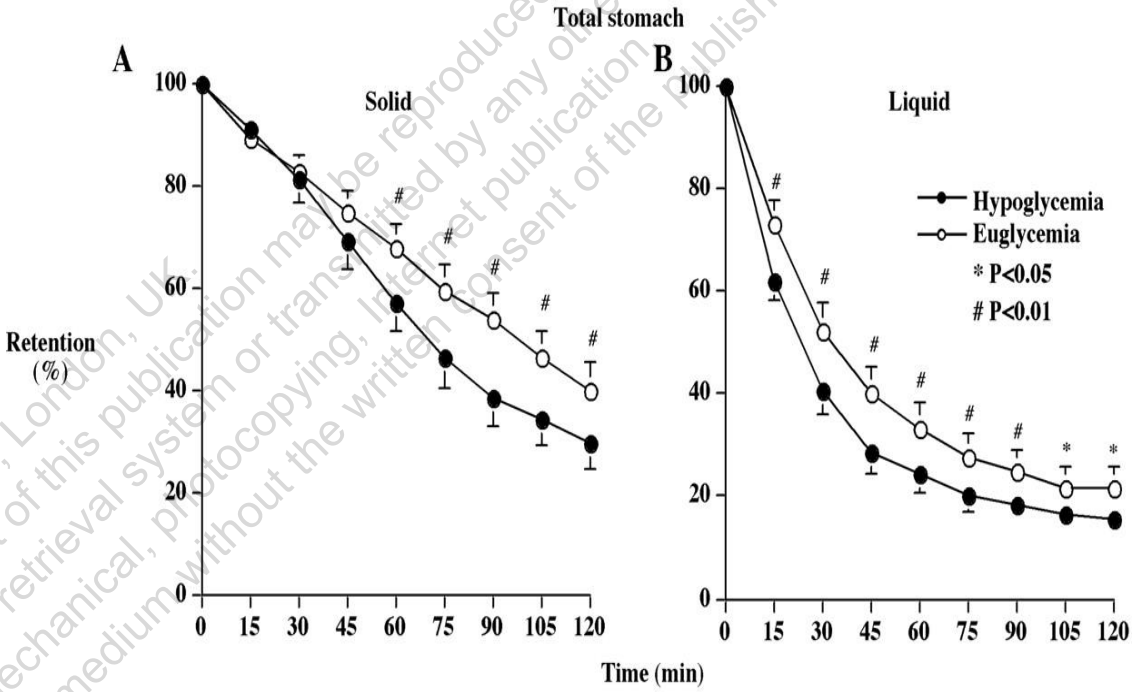
Most are asymptomatic

More frequent hypoglycaemic episodes prior to Coeliac diagnosis (Mohn et al, J Pediatr Gastro Nutr 2001)

No improvement of glycaemic control with gluten free diet (Kaukinen et al, Diabetes Care 1999)

# Gastric Emptying and Blood Sugar




**Blood sugar affects gastric emptying**

*Russo et al, J Clin Endocrin & Metab 2005*

**Hyperglycaemia delays gastric emptying**

*Samsom et al, Gut 1997*

**Miss X**
**born 1965, nurse**

Spouse: abusive and misusing alcohol
Work: isolated and unhappy

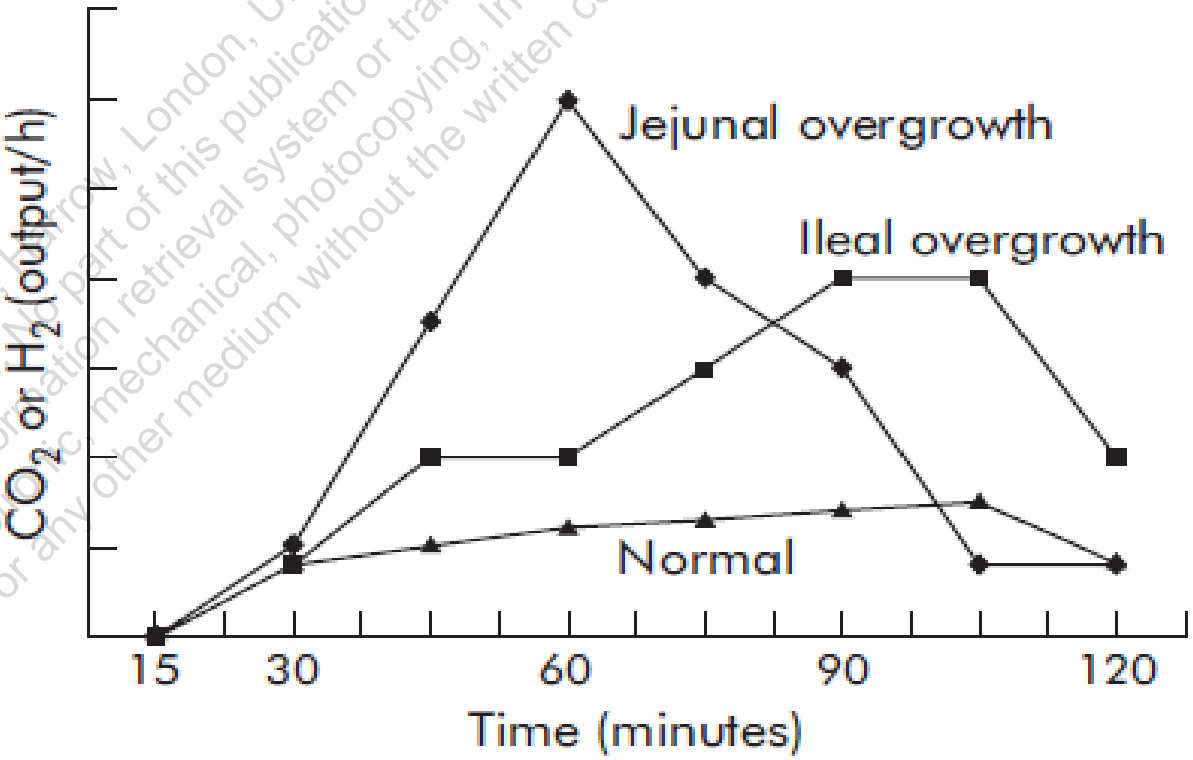
No overt psychological distress
No change after 3 months psychological input

# Investigating diabetic diarrhoea

Normal faecal elastase

Normal anorectal physiology

Breath test



# Miss X

Normal faecal elastase

Normal anorectal physiology

Breath test: positive

- started on doxycycline 100mg bd 1 week
- swift improvement in diarrhoea
- but recurred after 3 weeks
- started ciprofloxacin 500mg bd 1 week

-same outcome as before

- started cyclical antibiotics 1 week per month

# Miss X

Episodic diarrhoea still occurring 6 months later

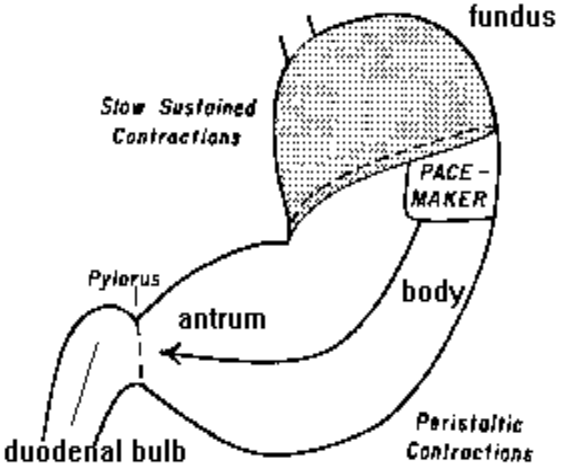
No response to loperamide or codeine

No response to cholestyramine

Subcutaneous octreotide 50-100μg 8-hourly (Nakabayashi et al, Arch Int Med 1994; Murao et al Endocr J 1999; Meyer et al, Int J Med 2003)

Marked response: switched to long-acting somatostatin (Corbould and Campbell, Diabet Med 2011)

# Altering fundal accommodation




$5HT_{1a}$ and muscarinic mediated :

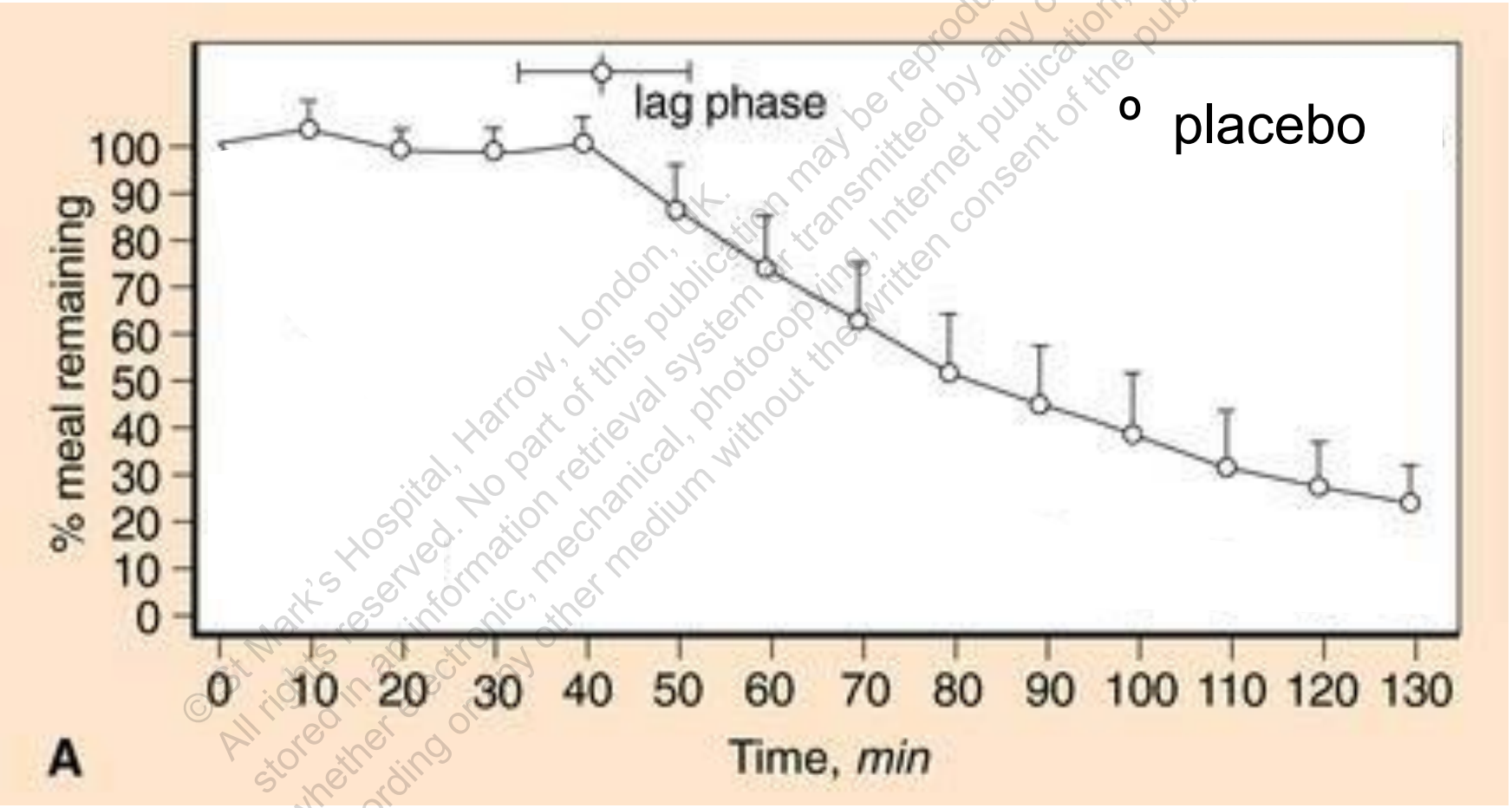
- buspirone: dose-dependent relaxation (man)
- acotiamide: dose-dependent relaxation (mouse)

Tricyclics/SSRIs are not as effective as in IBS

New motilin analogues becoming available

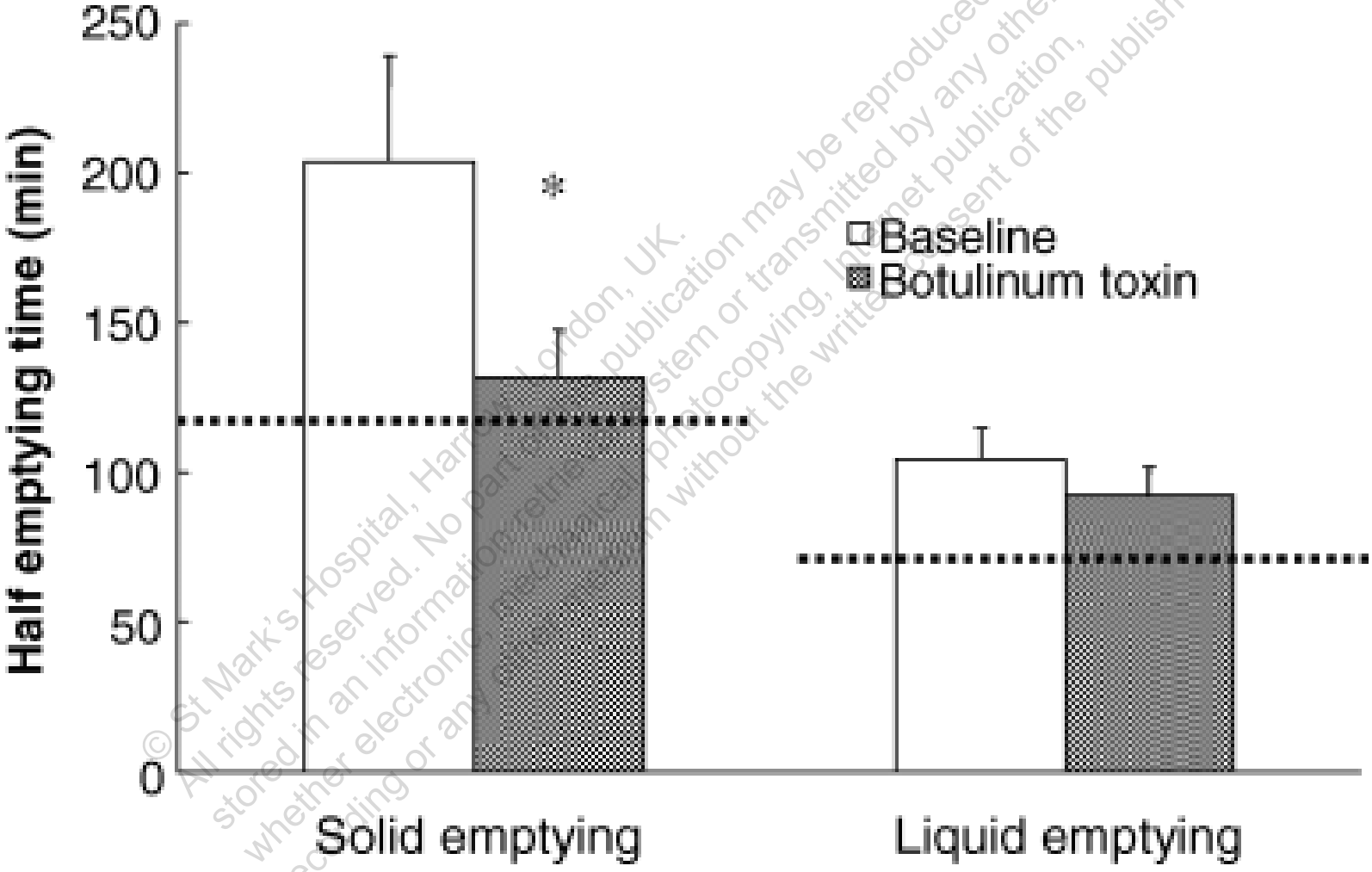
# Miss X

## Management



# Mechanical approaches to gastroparesis

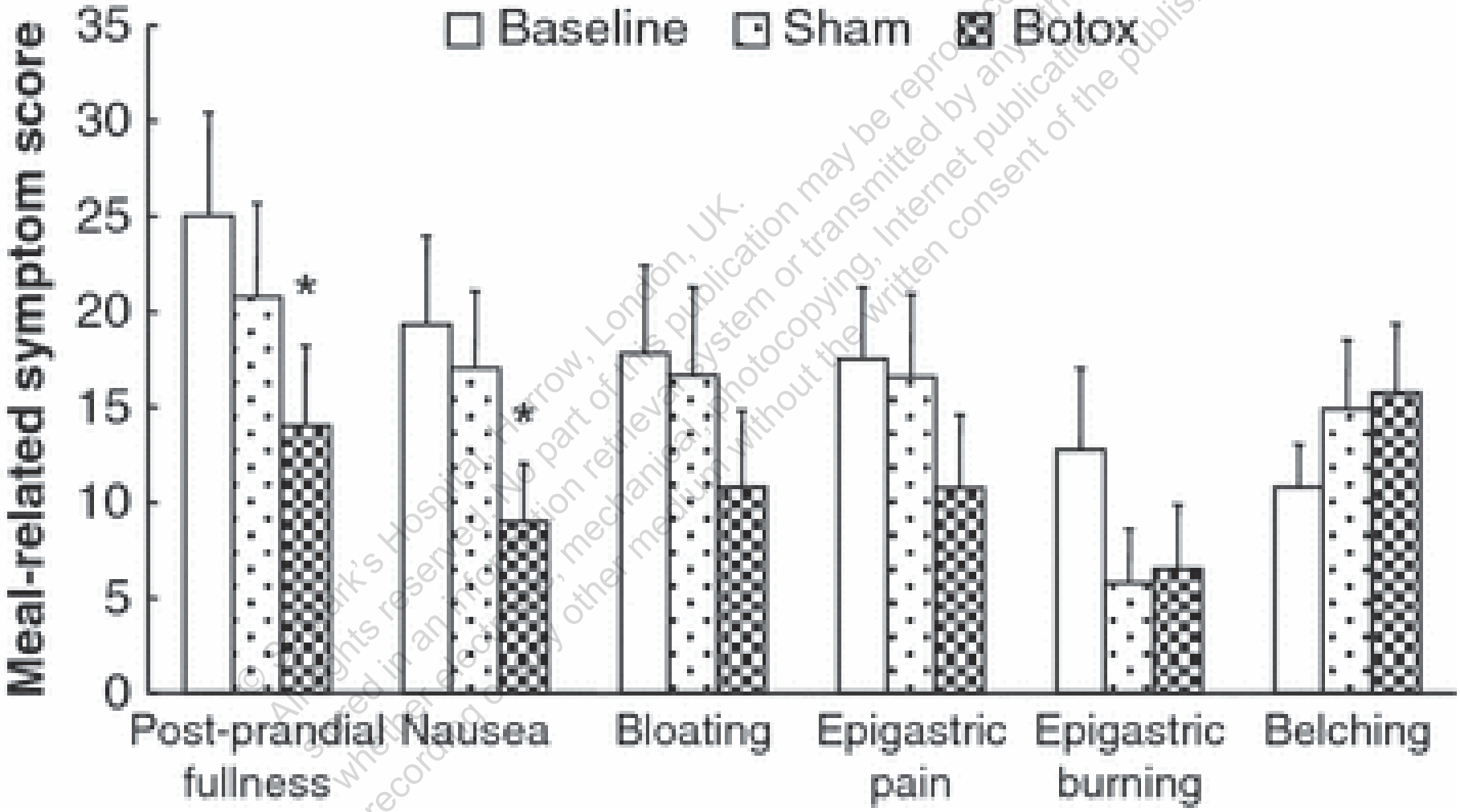
## Intrapyloric Botox in Diabetic Gastroparesis






Arts et al APT 2007

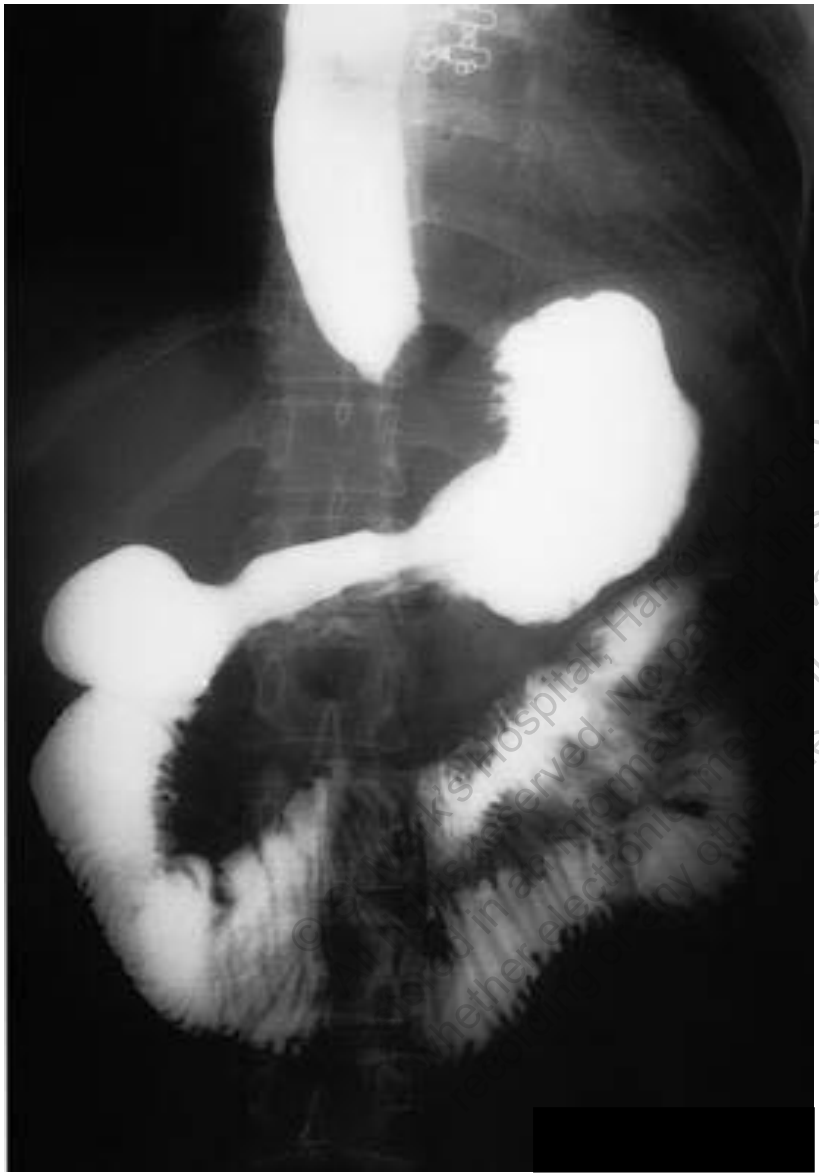
# Intrapyloric Botox in Diabetic Gastroparesis






Arts et al APT 2007

# Next



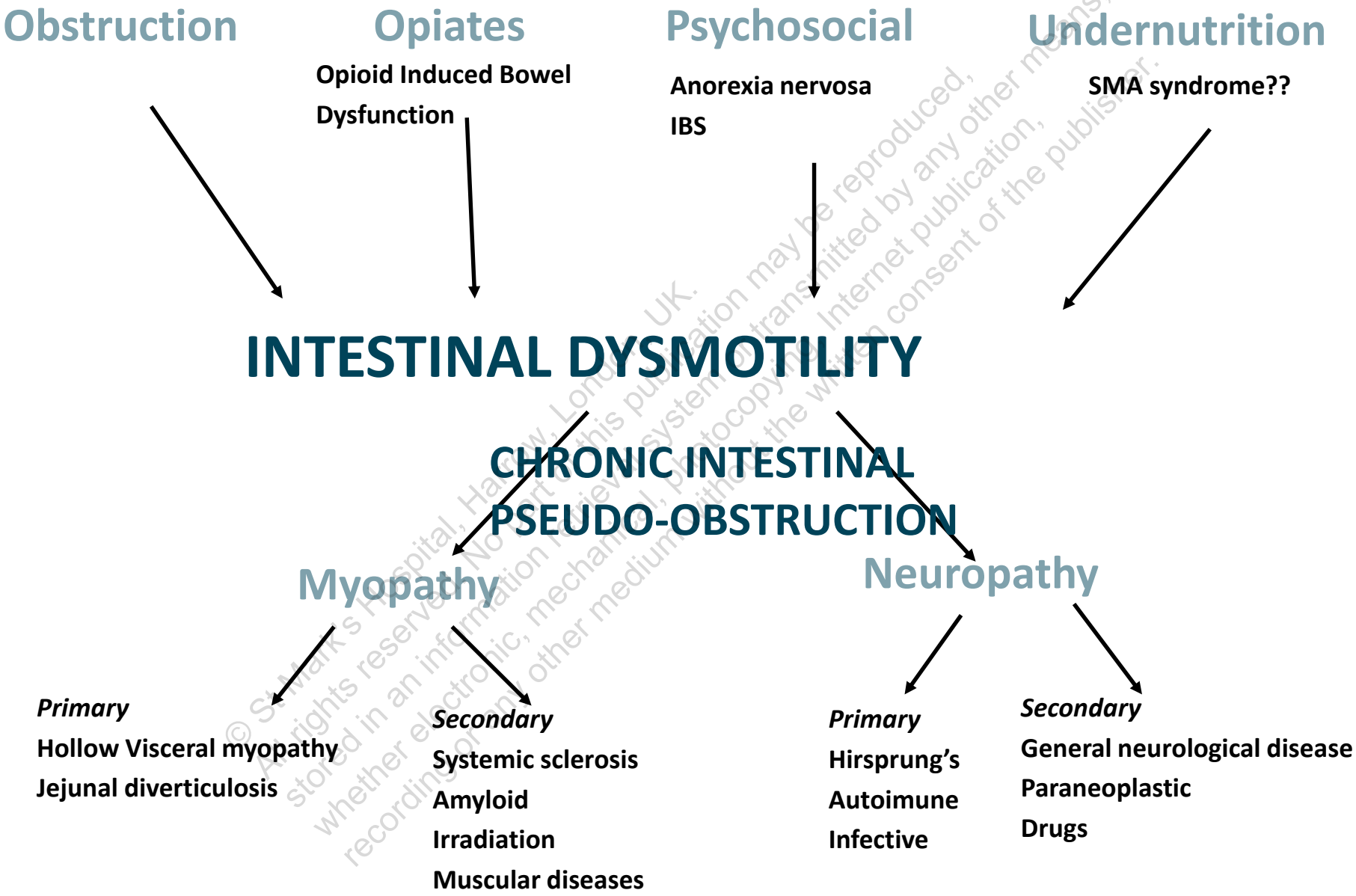
Key feature is **episodic** symptoms

Urinary symptoms common – especially myopathic forms

88% have un-necessary surgery before diagnosis

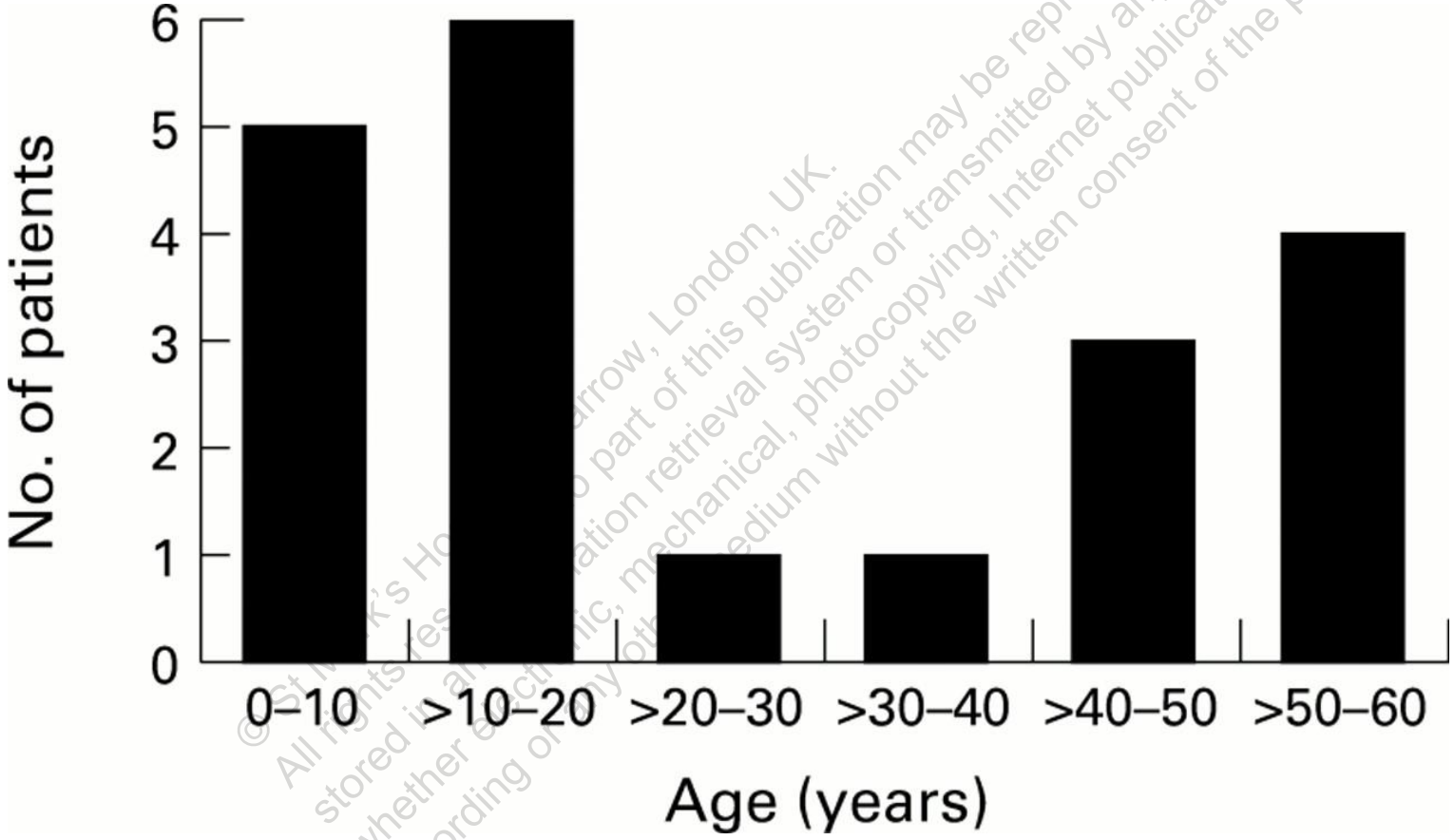
Mean 2.5 operations pre-diagnosis

8 years median time to diagnosis



# CIPO – clinical characteristics

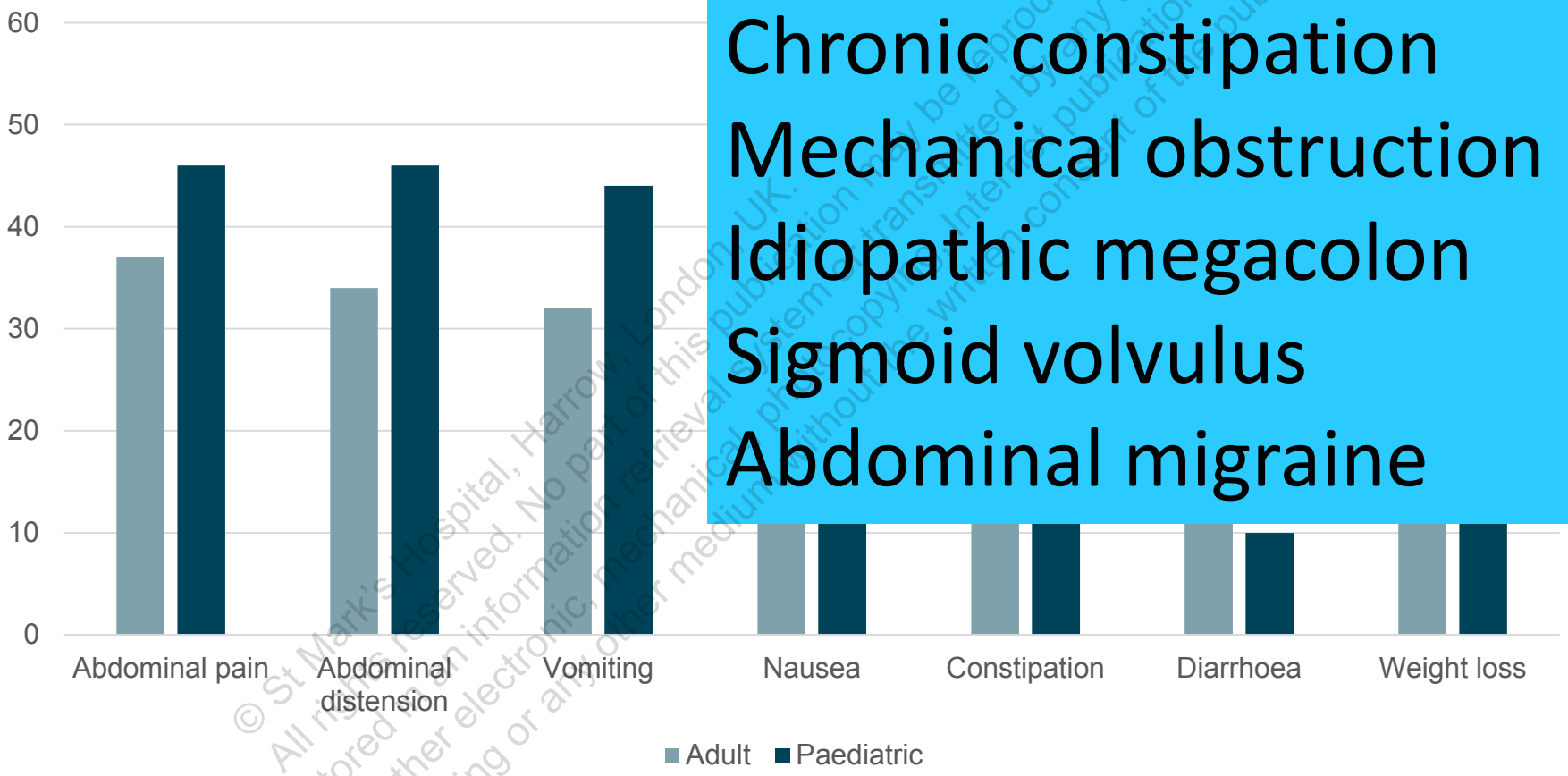
**Spectrum of age of onset of symptoms.**






Mann et al. Gut 1997;41:675-681

# CIPO symptoms




Missed diagnoses in 78%

Chronic constipation
Mechanical obstruction
Idiopathic megacolon
Sigmoid volvulus
Abdominal migraine



Mann et al. Gut 1997;41:675-681
Heyneke et al Arch Dis Child 1999; 81:21-27

# CIPO – initial history

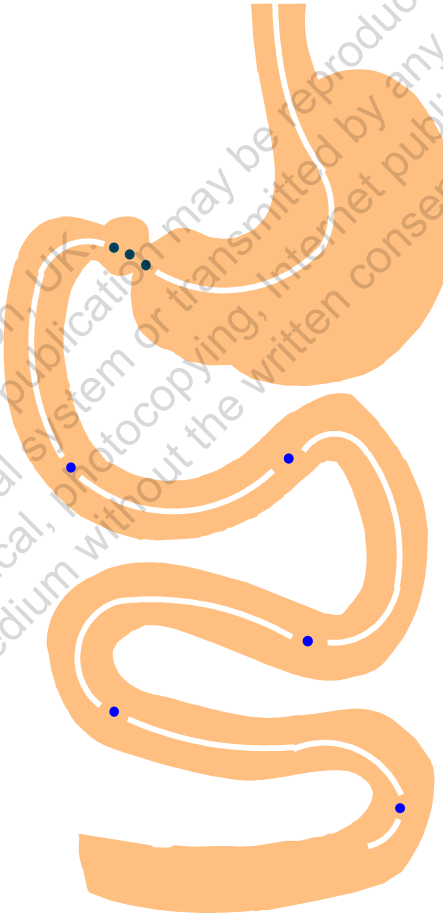
# INTESTINAL MANOMETRY

## RECORDING SITES

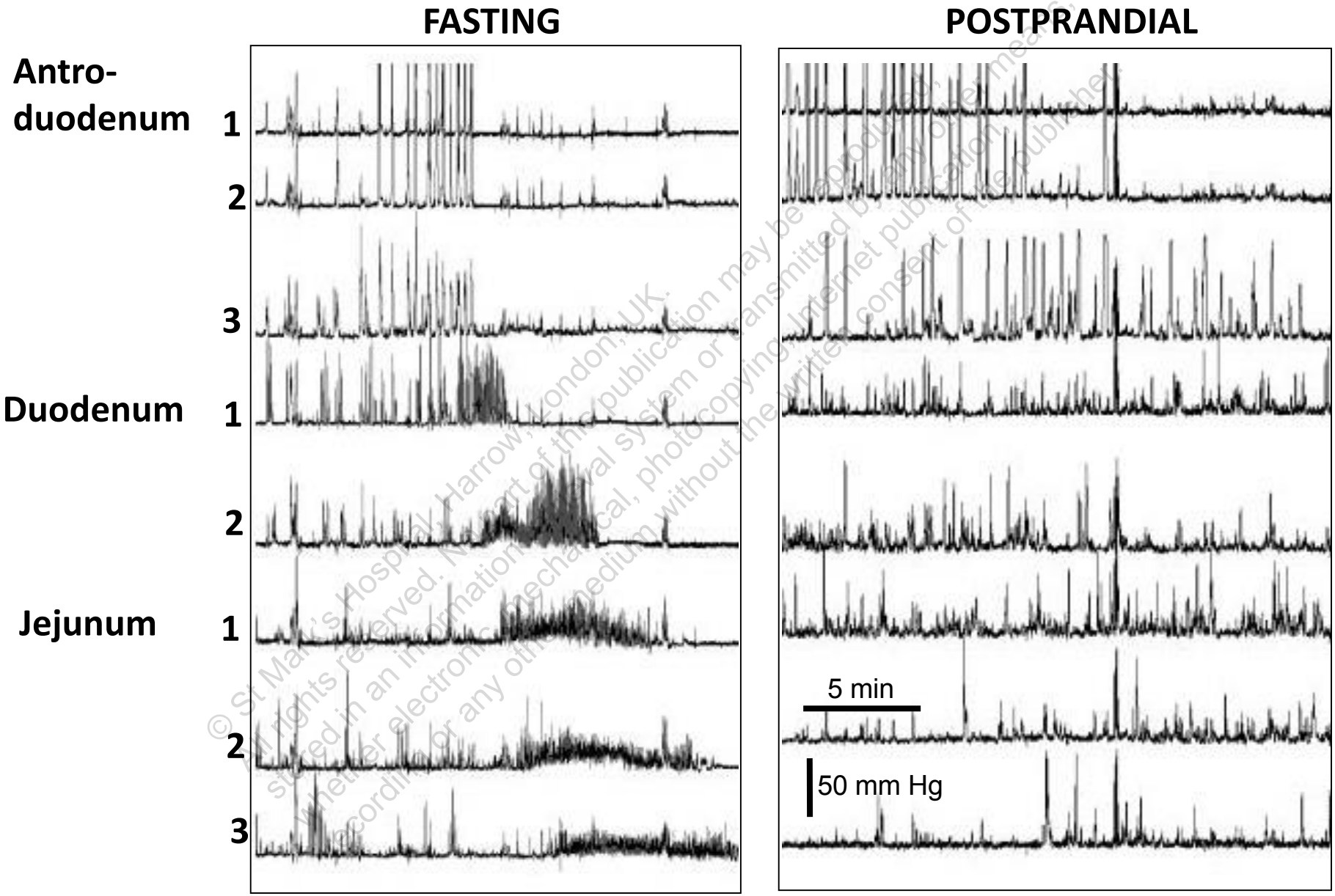
Antroduodenum

Duodenum

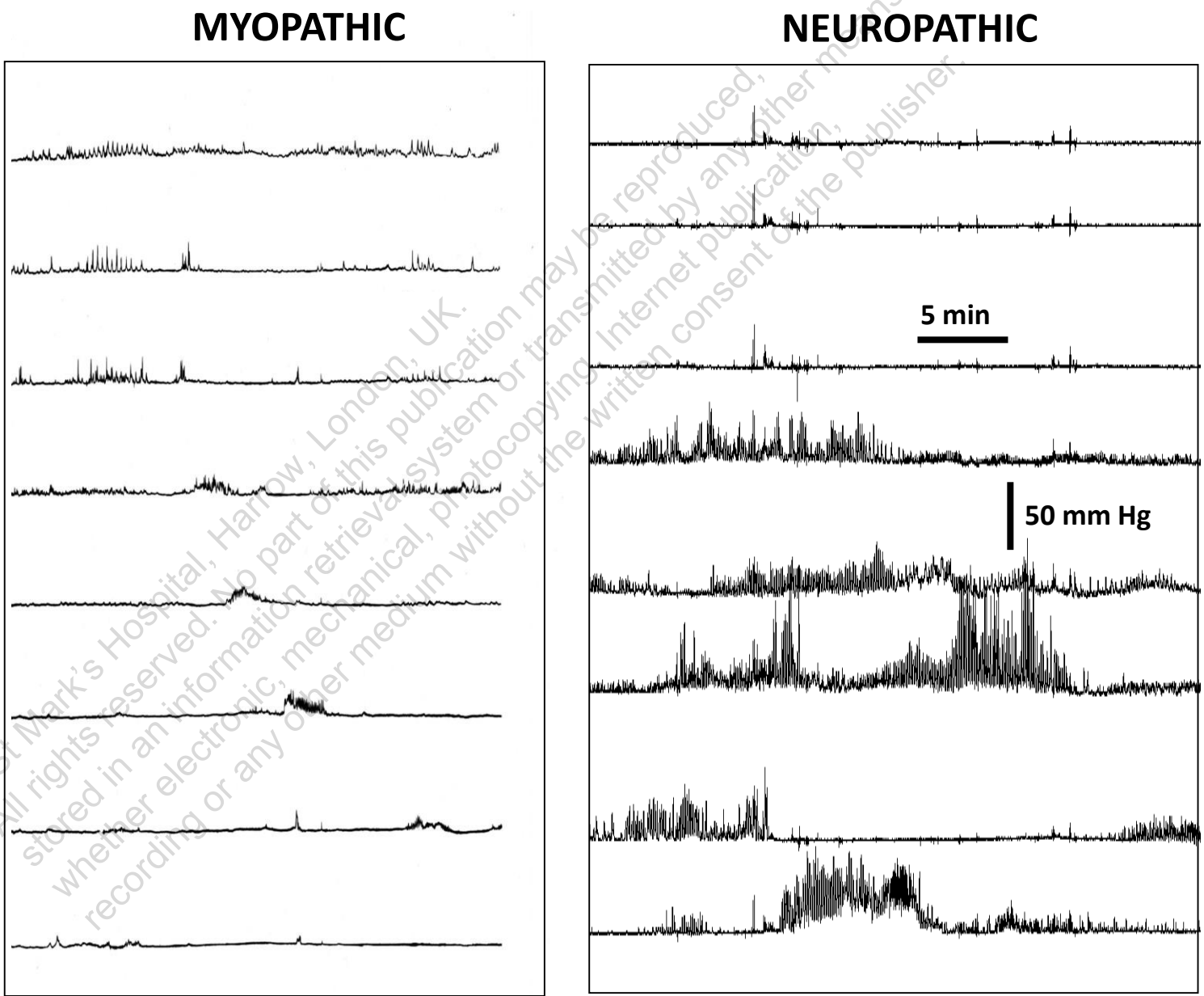
Jejunum



# Normal small bowel manometry



# Dysmotility patterns



# Is manometry of value?

**Table 3.** Predictive Value of Small Bowel Manometry for Poor Clinical Outcome at Follow-up in 59 Patients With CIIP

| Groups | SO FREQ | INADEQ M | PN | TRANSPL | Death | Pain |
|---|---|---|---|---|---|---|
| ABNAF | | | | | | |
| Absent (20) | 13 (65.0%) | 12 (60.0%) | 6 (30.0%) | 0 | 2 (10.0%) | 1 (5.0%) |
| Present (39) | 28 (71.8%) | 24 (61.5%) | 10 (25.6%) | 4 (10.3%) | 3 (7.7%) | 11 (28.2) |
| OR | 1.37 (0.43–4.34) | 1.07 (0.35–3.21) | 0.80 (0.24–2.66) | | 0.75 (0.11–4.89) | 7.46 (0.89–62.71) |
| *P* value | .812 | 1.000 | .962 | .349 | 1.000 | .079 |
| Bursts | | | | | | |
| Absent (24) | 15 (62.5%) | 9 (37.5%) | 2 (8.3%) | 2 (8.3%) | 3 (12.5%) | 3 (12.5%) |
| Present (35) | 26 (74.3%) | 27 (77.1%) | 14 (40.0%) | 2 (5.7%) | 2 (5.7%) | 9 (25.7%) |
| OR | 1.73 (0.56–5.32) | 5.73 (1.79–17.63) | 7.33 (1.48–36.24) | 0.66 (0.09–5.09) | 0.42 (0.06–2.76) | 2.42 (0.58–10.01) |
| *P* value | .498 | .005 | .017 | 1.000 | .657 | .363 |
| NO-FED | | | | | | |
| Absent (53) | 16 (30.2%) | 31 (58.5%) | 13 (24.5%) | 4 (7.5%) | 4 (7.5%) | 8 (15.1%) |
| Present (6) | 2 (33.3%) | 5 (83.3%) | 3 (50%) | 0 | 1 (16.7%) | 4 (66.7%) |
| OR | 0.86 (0.14–5.21) | 3.55 (0.39–32.52) | 3.08 (0.55–17.15) | | 2.45 (0.23–26.38) | 11.25 (1.76–72.92) |
| *P* value | 1.000 | .459 | .398 | 1.000 | 1.000 | .015 |
| Hypomotility | | | | | | |
| Absent (47) | 34 (72.3%) | 30 (63.8%) | 13 (27.7%) | 3 (6.4%) | 1 (2.1%) | 9 (19.1%) |
| Presen (12) | 5 (41.7%) | 6 (50.0%) | 3 (25.0%) | 1 (8.3%) | 4 (33.3%) | 3 (25.0%) |
| OR | 0.53 (0.14–1.99) | 0.57 (0.16–2.03) | 0.87 (0.20–3.73) | 1.33 (0.13–14.09) | 23.00 (2.27–233.18) | 1.41 (0.32–6.28) |
| *P* value | .556 | .586 | 1.000 | 1.000 | .004 | .962 |
| Clusters | | | | | | |
| Absent (39) | 28 (71.8%) | 23 (59.0%) | 10 (25.6%) | 4 (10.3%) | 4 (10.3%) | 7 (17.9%) |
| Presen (20) | 13 (65.0%) | 13 (65.0%) | 6 (30.0%) | 0 | 1 (5.0%) | 5 (25.0%) |
| OR | 0.72 (0.23–2.31) | 1.29 (0.42–3.95) | 1.24 (0.38–4.11) | | .46 (0.05–4.42) | 1.52 (0.41–5.60) |
| *P* value | | | | | | .962 |

INADEQ M, inability to maintain a normal diet; PN, parenteral nutrition; TRANSPL, transplantation; SO FREQ, frequency of episodes suggestive of subacute intestinal obstruction; Clusters, clustered contractions.

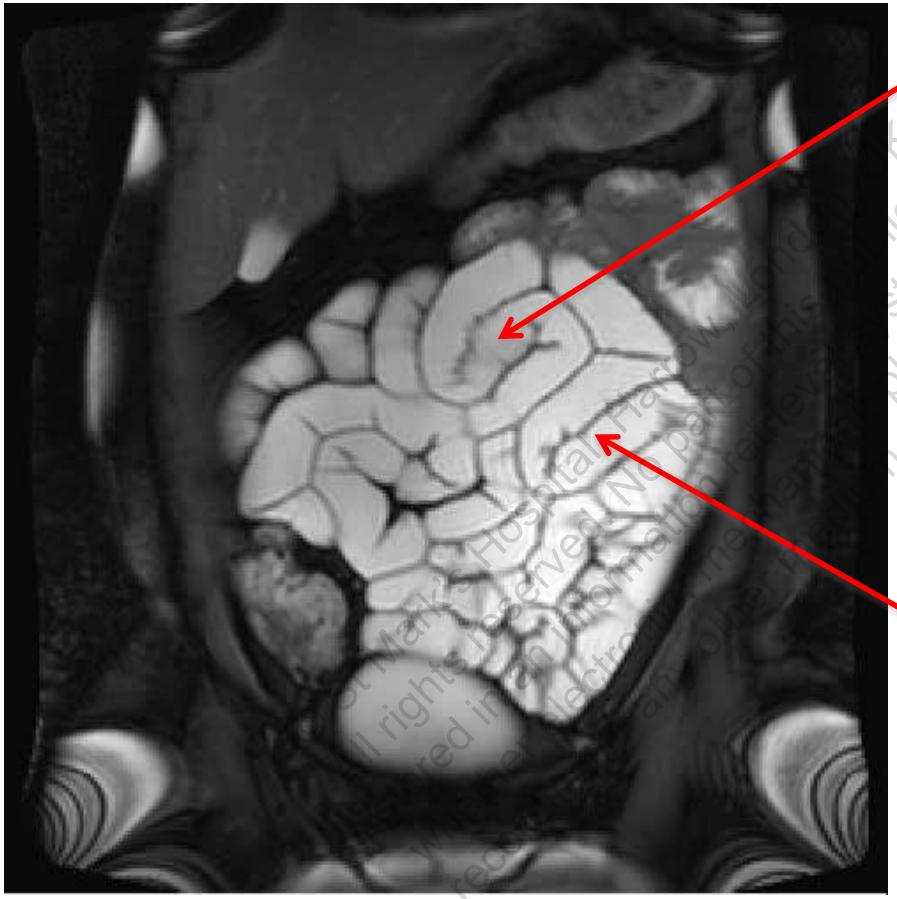


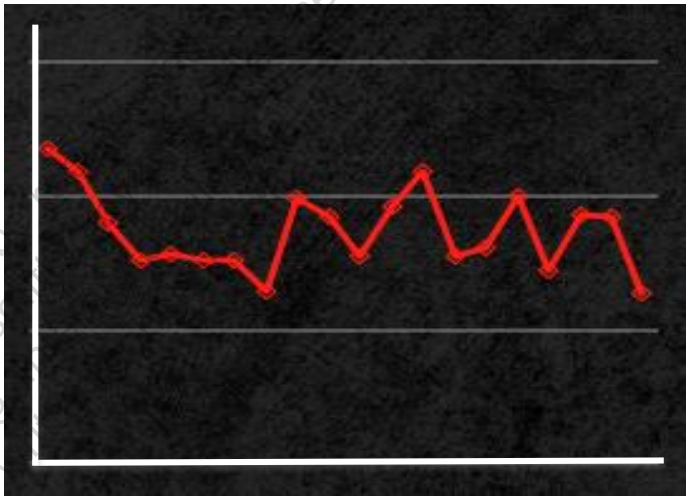
**Stanghellini et al. Clin Gastro Hepatol 2005: 3: 449-58**

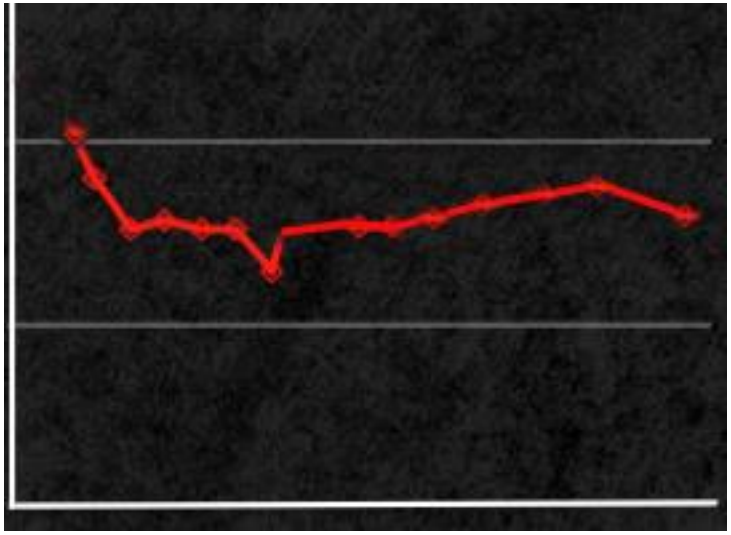
# Small bowel MRI

## Motility analysis

**Unreliable for looking at global motility as the bowel is heterogeneous in how it contracts**



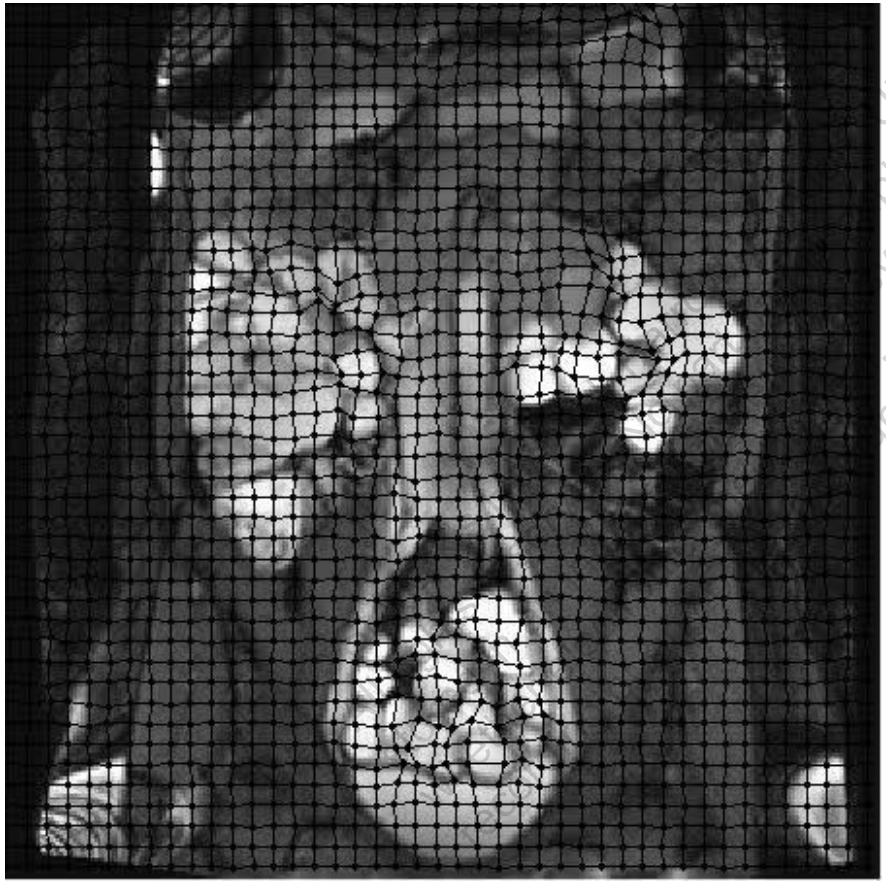


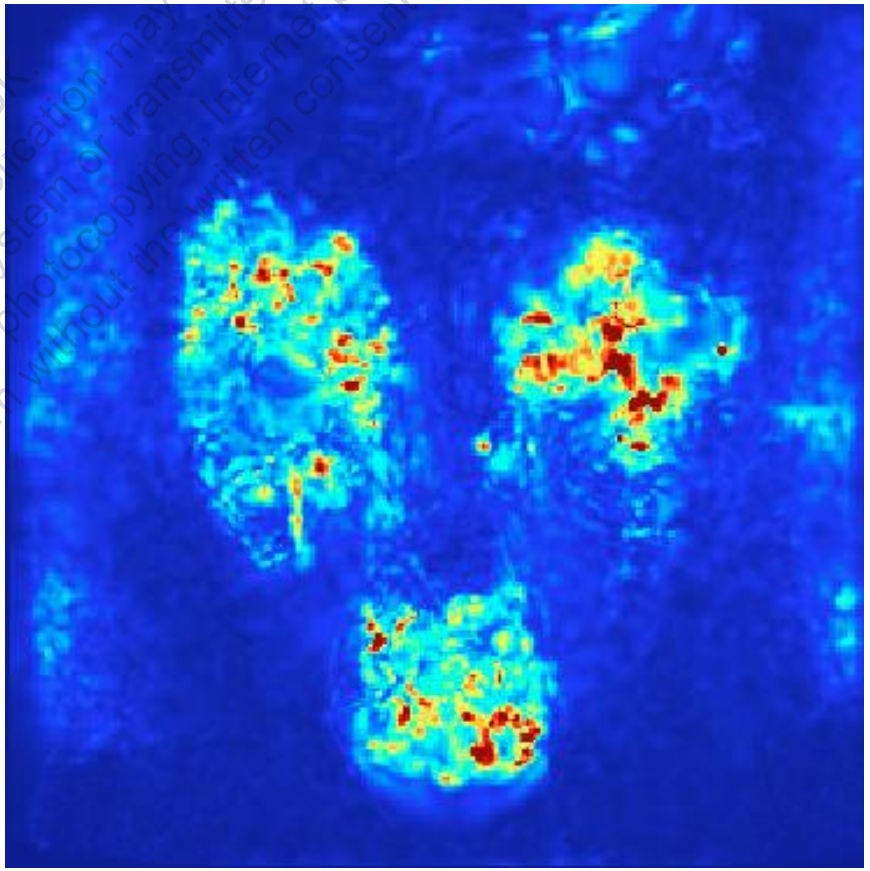



# Small bowel MRI

## Parametric maps

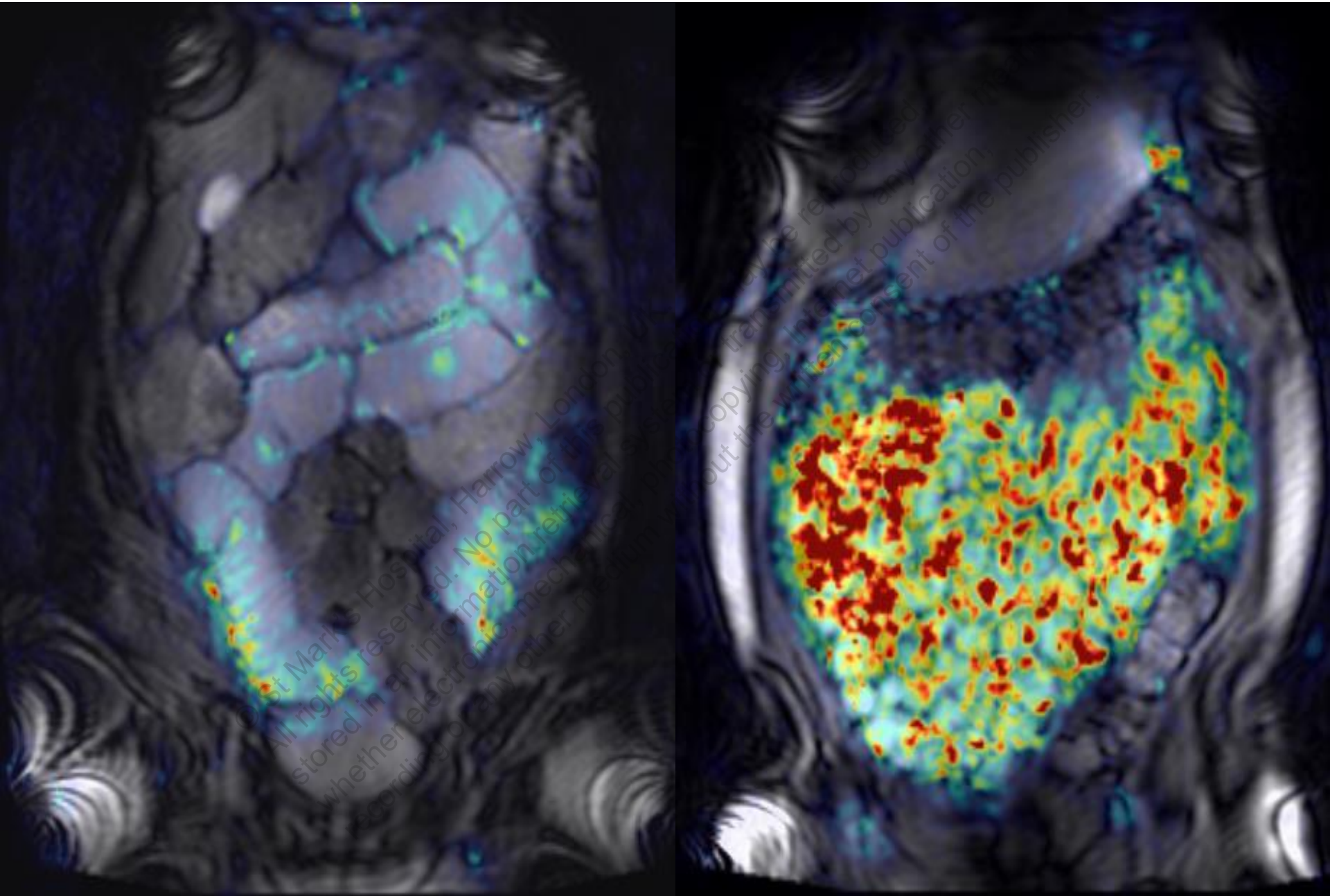
- Over each region of interest a grid can be placed which demonstrates how each small square of the bowel is moving
- This can be used to generate a motility map on the right which quantifies each squares motility





CIPO

Control



# Results –Mean baseline small bowel motility scores

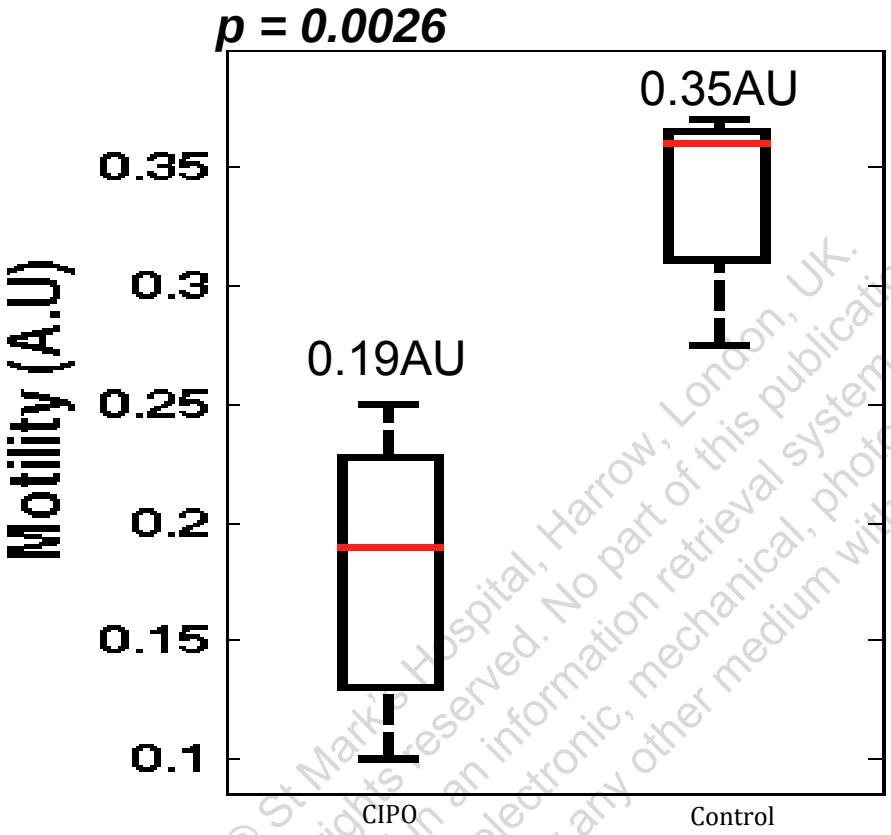



***Figure 1**. mean global motility difference in CIPO and control groups.*

CIPO patients had significantly decreased motility scores

Butt et al, UEG 2016

# Bacterial Overgrowth in CIPO

21/22 paediatric patients recurrent bacterial overgrowth (Goulet, Eur J Pediatr Surg)

Jejunal aspirate vs Hydrogen breath test

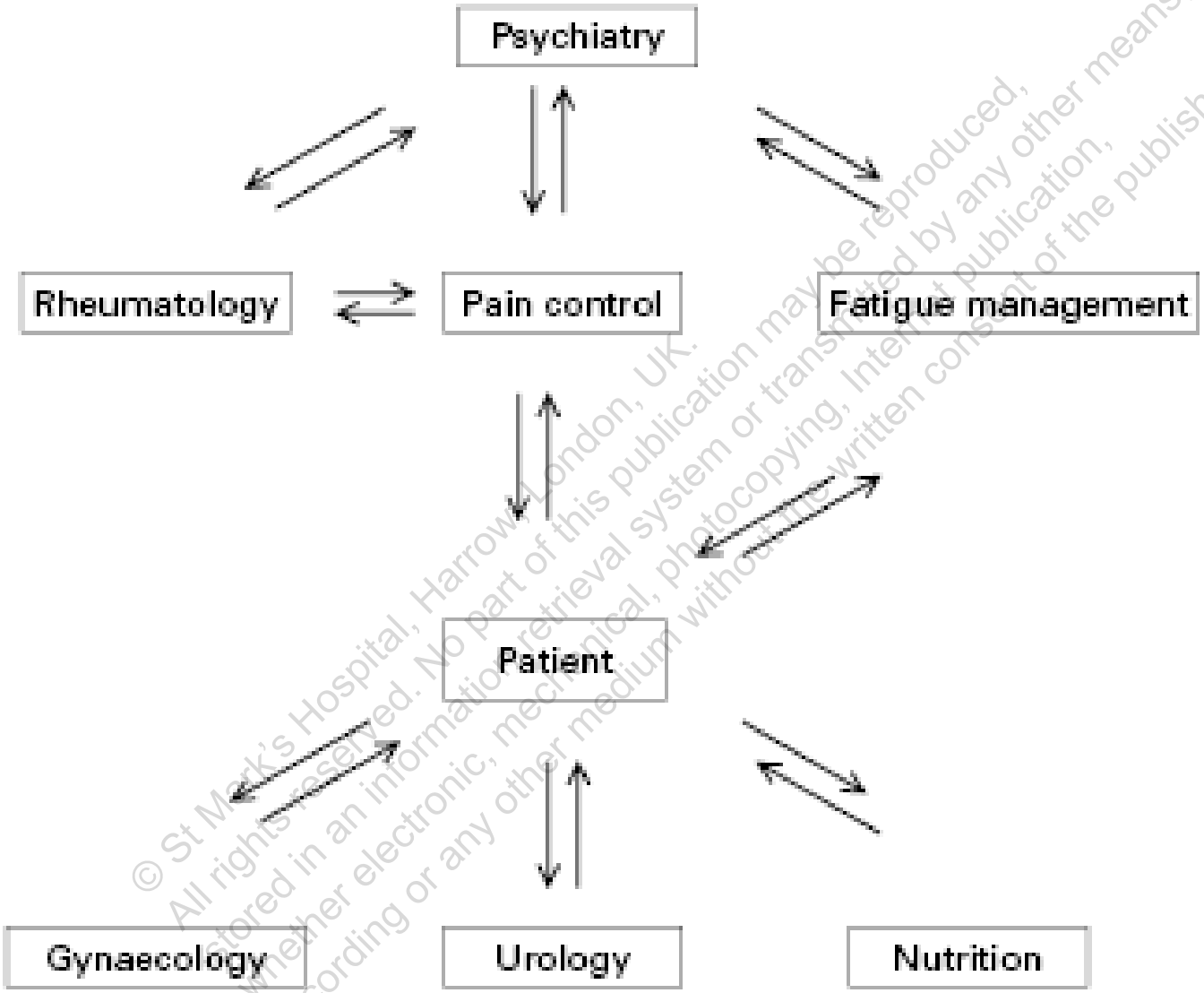
Evidence for:

- metronidazole 400mg bd 1 week
- ciprofloxacin 500mg bd 5-10 days
- doxycycline 100mg bd 1 week

Most patients need recurrent courses

Rotating cycles of antibiotic prophylaxis (Bures et al, World J Gastro 2010:16 2978-80)

# Multidisciplinary problem



# Psychological issues

Delay in diagnosis

Ignorance in medical community

No cure

Pain = key symptom, problems of analgesia (side effects, addiction)

Impact on family, carers, job → self esteem/confidence /mood

Anxiety, depression, somatisation, poor coping, sickness role

# Prokinetics for severe dysmotility / CIPO

## Cisapride

1 physiological study

- accelerates transit

3 case reports

- benefit: 6-24 months

1 case report

- worsened symptoms

## Neostigmine

Unequivocal benefit in acute pseudo-obstruction

Case reports benefit in CIPO

- $2^{o}$ paraneoplastic state
- Systemic sclerosis

Cautions:

1. Cholinergic crisis
2. Needs ECG monitoring

Use 1 to 2mg boluses

# Results data -Mean % increase in small bowel motility scores following neostigmine:

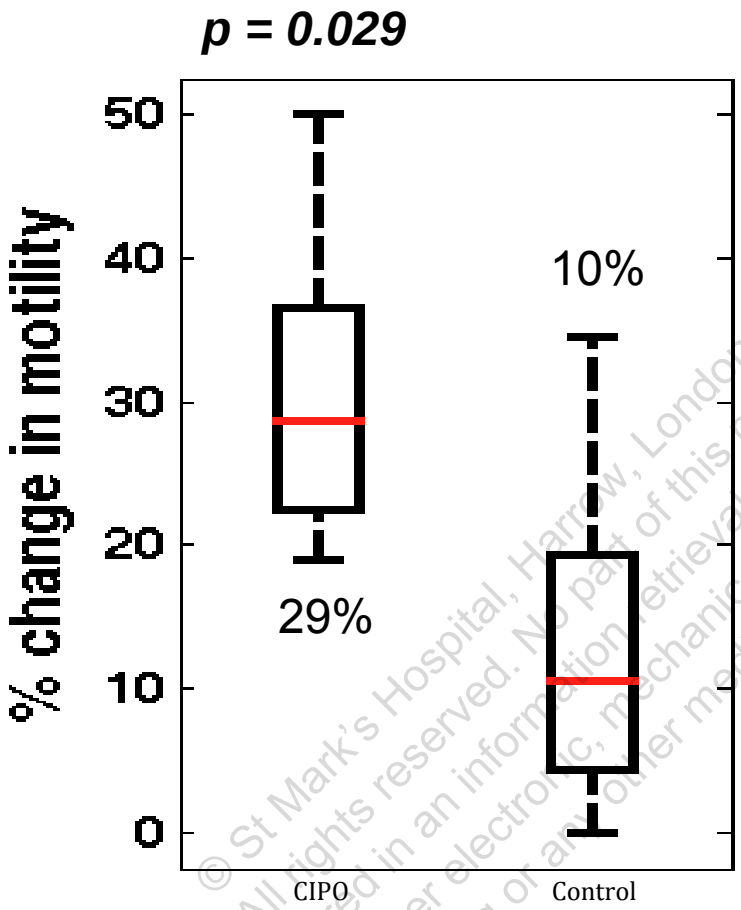



***Figure 2**. % change in motility between CIPO and control groups*

CIPO patients had a significant increase in motility score with neostigmine compared to controls

Butt et al, UEG 2016

# Prokinetics

## Erythromycin

15 patients with small bowel dilatation

All given erythromycin orally (9 initially IV)

6/15 patients responded (↓ pain and vomiting)

- 5/6 male (vs 1/9 male non-responders)
- 0/6 chronic opiate use (vs 4/9 non-responders)



*Shand et al (APT 2005)*

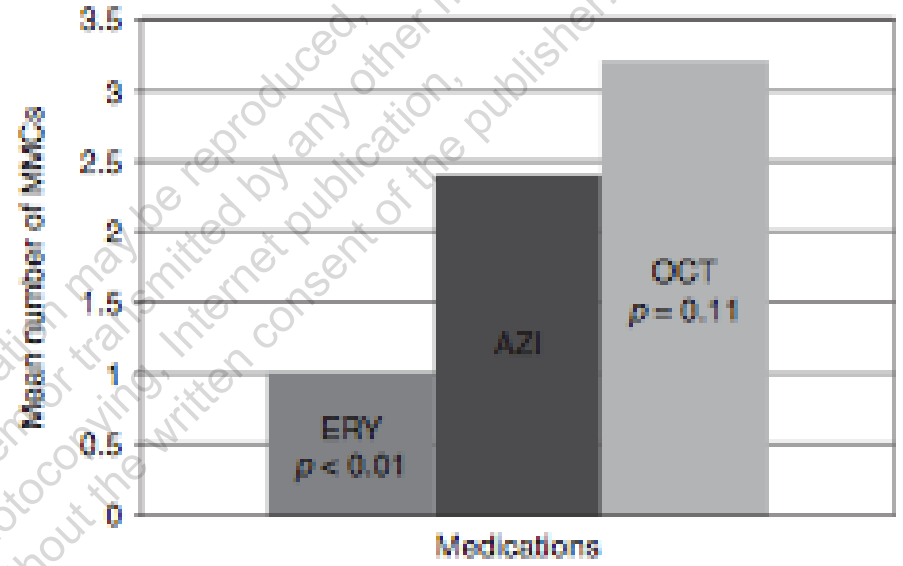
# Azithromycin as a potentially more potent alternative to erythromycin

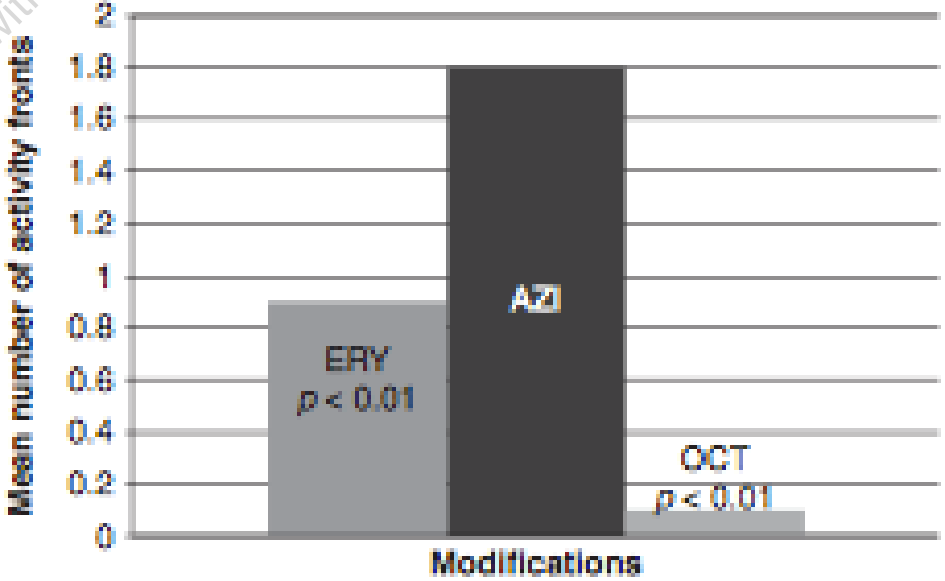
n=21 with manometric dysmotility

Cross-over type design

- erythromycin 250mg iv
- azithromycin 250mg iv
- octreotide 50μg sc

No symptom data



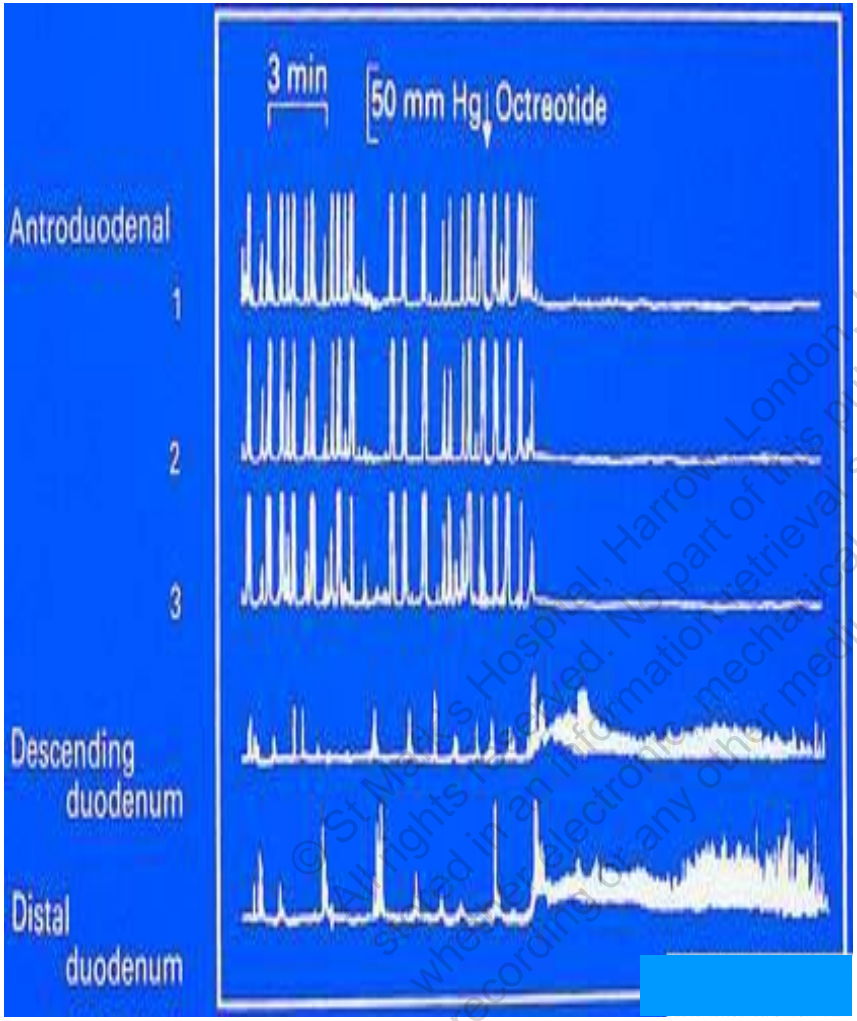






Chini et al., Scan J Gastroenterol 2012

# Prokinetics

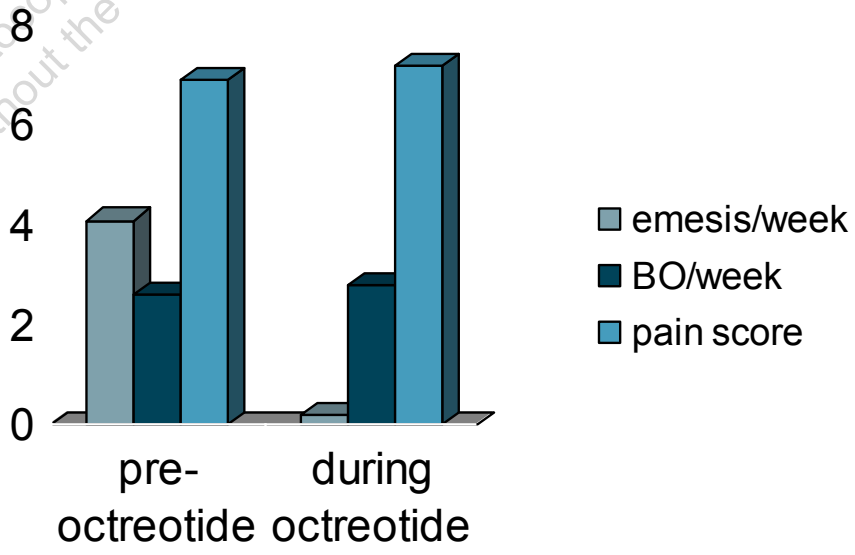
## Octreotide




Possible prokinetic effect

5 patients with dysmotility

*Soudah et al (NEJM) 2000*



# Enteric feed intolerance - Post-operative ileus

Occurs after 19% abdominal surgeries

Mean length of stay 11.5 vs 5.5 days (with vs without ileus)

Mean cost $18,877 vs $9,460 (with vs without ileus)

Goldstein et al, P & T 2007

Treatment:

- Restore normal physiology
- Insert nasogastric tube
- Accurately measure fluid input and output
- Exclude and treat secondary causes
- Nutritional input if prolonged
- Erythromycin & metoclopramide no use (Cochrane 2008)

# Mosapride in post-operative ileus

**Table 3. Outcome variables in patients receiving mosapride after hand-assisted laparoscopic colectomy compared with controls**

| | *Mosapride (n=20)* | *Control (n=20)* | *P value* |
|---|---|---|---|
| Postoperative time (hours) to | | | |
| First flatus | 32.7 (20.6–48.5) | 39.1 (16.7–58.0) | 0.2793 |
| First bowel movement | 48.5 (22.9–69.7) | 69.3 (17.3–122.0) | 0.0149 |
| Postoperative hospital stay (days) | 6.7 (5–19) | 8.4 (6–19) | 0.0398 |
| Tmax (min) | | | |
| 24 hours | 36.3 (20–80) | 38.3 (20–100) | 0.7868 |
| 48 hours | 27.9 (20–50) | 35.3 (20–50) | 0.0294 |
| Number of patients with nausea | 0 | 1 | >0.9999 |
| Number of patients with vomiting | 0 | 0 | |

Tmax = time to maximal gastric emptying rate as determined by [$^{13}$C]-acetate breath test. • Unless otherwise specified, data are means with ranges in parentheses. • Comparisons regarding postoperative time, hospital stay, and Tmax were made by using the Mann-Whitney *U* test.



Narita et al, DCR 2008

# Mosapride for post-operative ileus

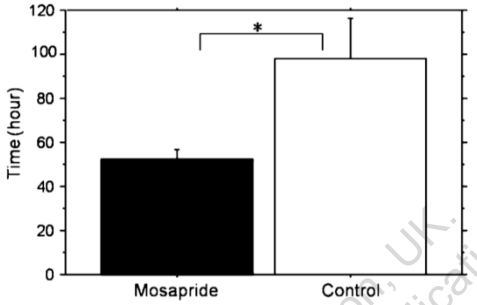



**Fig. 1** Time to the appearance of first flatus after surgery in the mosapride group and the control group. *$P$<0.05

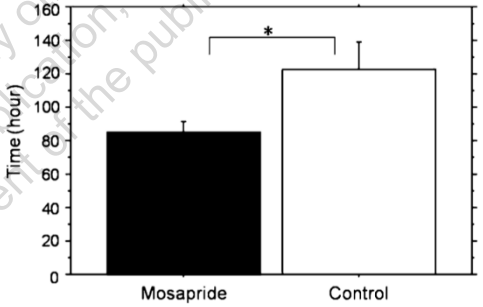



**Fig. 2** Time to the appearance of first defecation after surgery in the mosapride group and the control group. *$P$<0.05

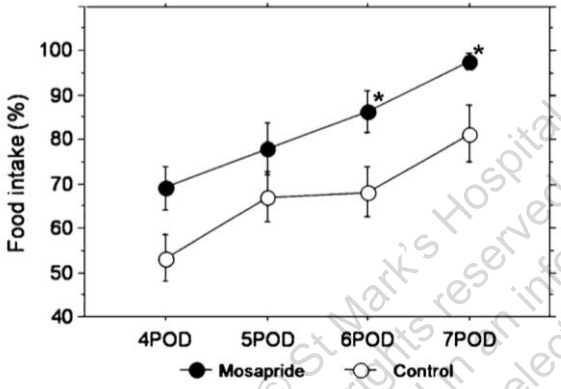
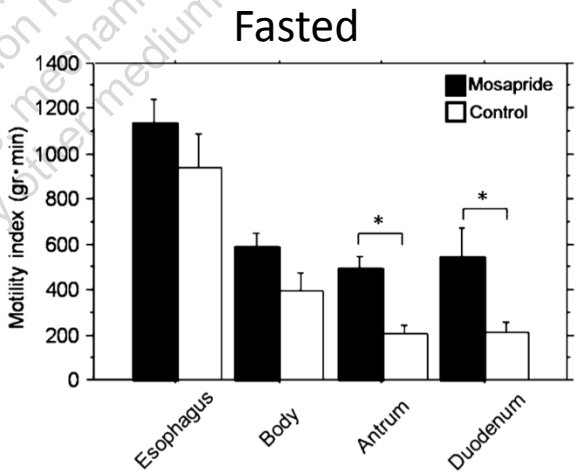
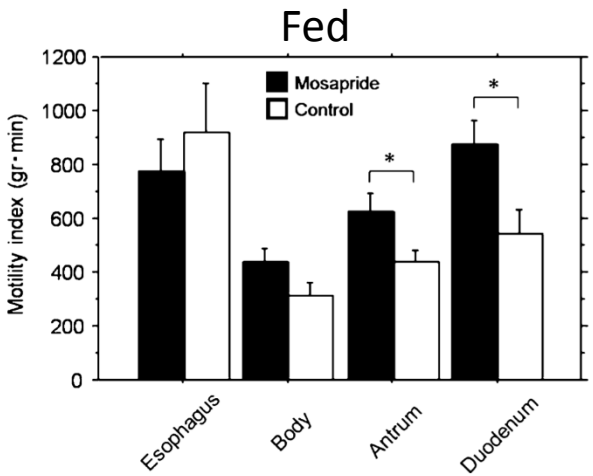



**Fig. 3** Changes in the amount of food intake in the mosapride group and the control group. *$P$<0.05



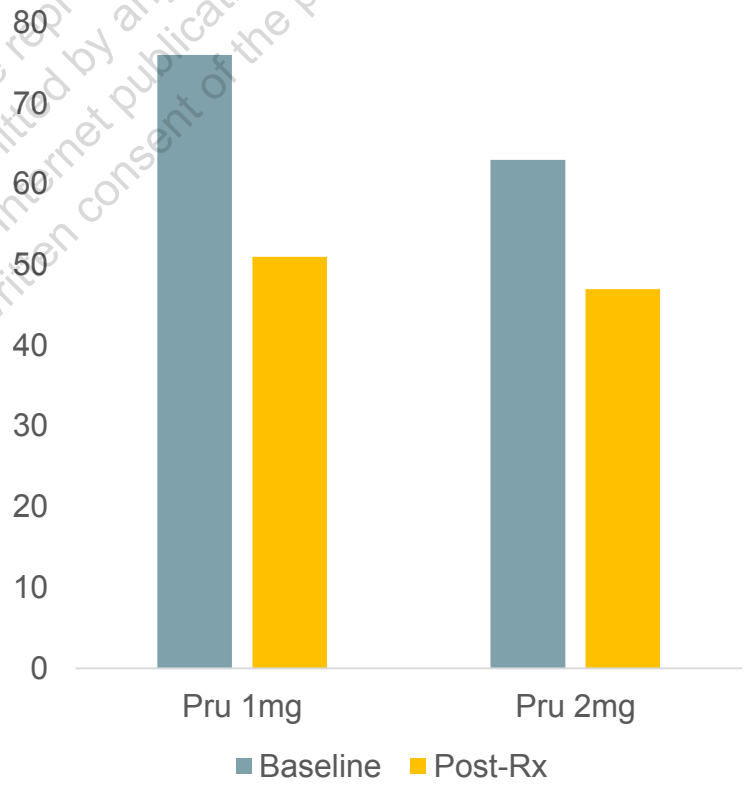






Toyomasu et al, J Gastrointest Surg 2011

# Prucalopride – small bowel transit

| | Intention-to-treat | | |
|---|---|---|---|
| | Placebo ($n = 36$)‡ | Prucalopride ($n = 37$) | *P* value |
| Average weekly frequency of spontaneous bowel movements* | | | |
| Baseline | 5.7 ± 4.4 | 5.9 ± 5.8 | N.S. |
| End of treatment | 5.0 ± 3.6 | 7.6 ± 5.7 | 0.019 |
| Change | − 0.7 ± 2.6 | 1.8 ± 2.7 | < 0.001 |
| Time to first spontaneous bowel movement (h.min)† | | | |
| 25th quartile | 6.30 | 1.20 | |
| 50th quartile | 24.20 | 3.50 | |
| 75th quartile | 69.00 | 23.55 | < 0.001 |






Emmanuel et al, APT 2002

Emmanuel et al, Gut 1998

# Prucalopride – small bowel transit

**Table 2.** Gastric, Small Bowel, and Colonic Transit

| | n | GE[a] (*min*) | SBTT[a] (*min*) | GC4[a] | GC24 | GC48 |
|---|---|---|---|---|---|---|
| Placebo | 14 | 117 ± 6 | 217 ± 20 | 0.6 ± 0.1 | 2.3 ± 0.3 | 3.1 ± 0.3 |
| PRU 2 mg | 13 | 105 ± 5 | 155 ± 14 | 1.0 ± 0.2 | 2.5 ± 0.2 | 3.8 ± 0.3 |
| PRU 4 mg | 11 | 92 ± 5[b] | 138 ± 15[b] | 1.6 ± 0.2[b] | 3.2 ± 0.4[b] | 3.8 ± 0.3 |

NOTE. Data are expressed as mean ± SEM.

GE, gastric emptying t½; SBTT, small bowel transit time t10%; GC, geometric center at 4 (GC4), 24 (GC24), and 48 (GC48) hours.

[a]Overall significance for PRU vs. placebo for the transit parameters ($P < 0.05$).

[b]Difference ($P < 0.05$) for 4 mg PRU vs. placebo.



Bouras et al, Gastroenterol 2001

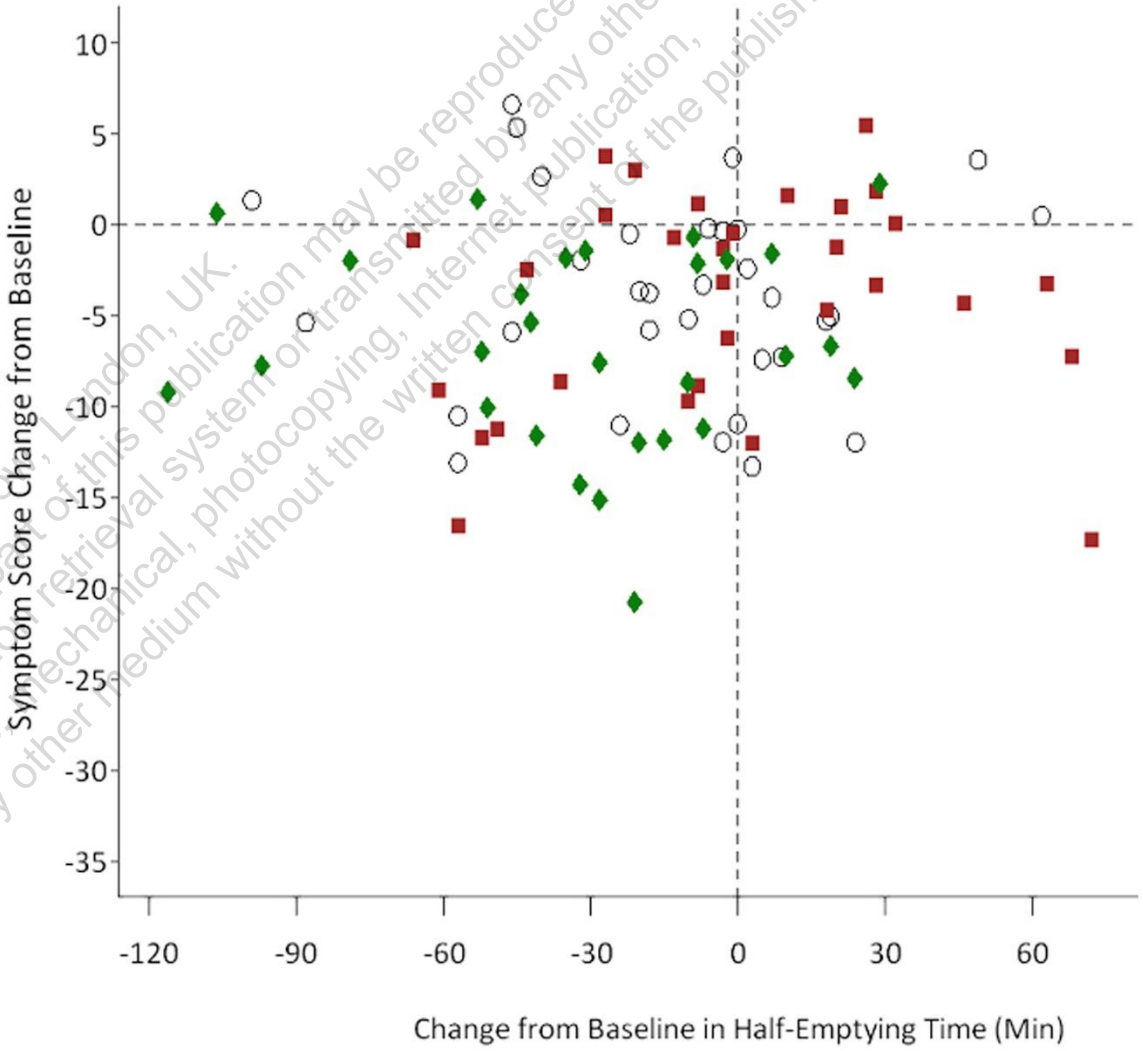
# Relamorelin

204 patients with DM + vomiting at baseline

| Treatment | N | Baseline mean (SE) | Change from baseline | | Difference from placebo | |
|---|---|---|---|---|---|---|
| | | | LS mean | *P* value | LS mean (95% CI) | *P* value |
| mITT population | | | | | | |
| Placebo | 61 | 126.8 | -7.5 | .0925 | - | - |
| Relamorelin 10 μg once daily evening | 58 | 126.0 | -5.9 | NS | 1.6 (-10.9 to 14.2) | NS |
| Relamorelin 10 μg twice daily | 59 | 126.8 | -22.9 | <.001 | -15.4 (-27.9 to -2.9) | .0307 |
| Vomiting subgroup | | | | | | |
| Placebo | 36 | 130.7 (6.2) | -5.6 | - | - | - |
| Relamorelin 10 μg once daily evening | 33 | 125.8 (7.3) | -2.2 | NS | 3.4 (-15.0 to 21.7) | NS |
| Relamorelin 10 μg twice daily | 30 | 123.2 (7.2) | -30.6 | <.001 | -25.0 (-43.9 to -6.1) | .019 |

Lembo et al 2016 Gastroenterol

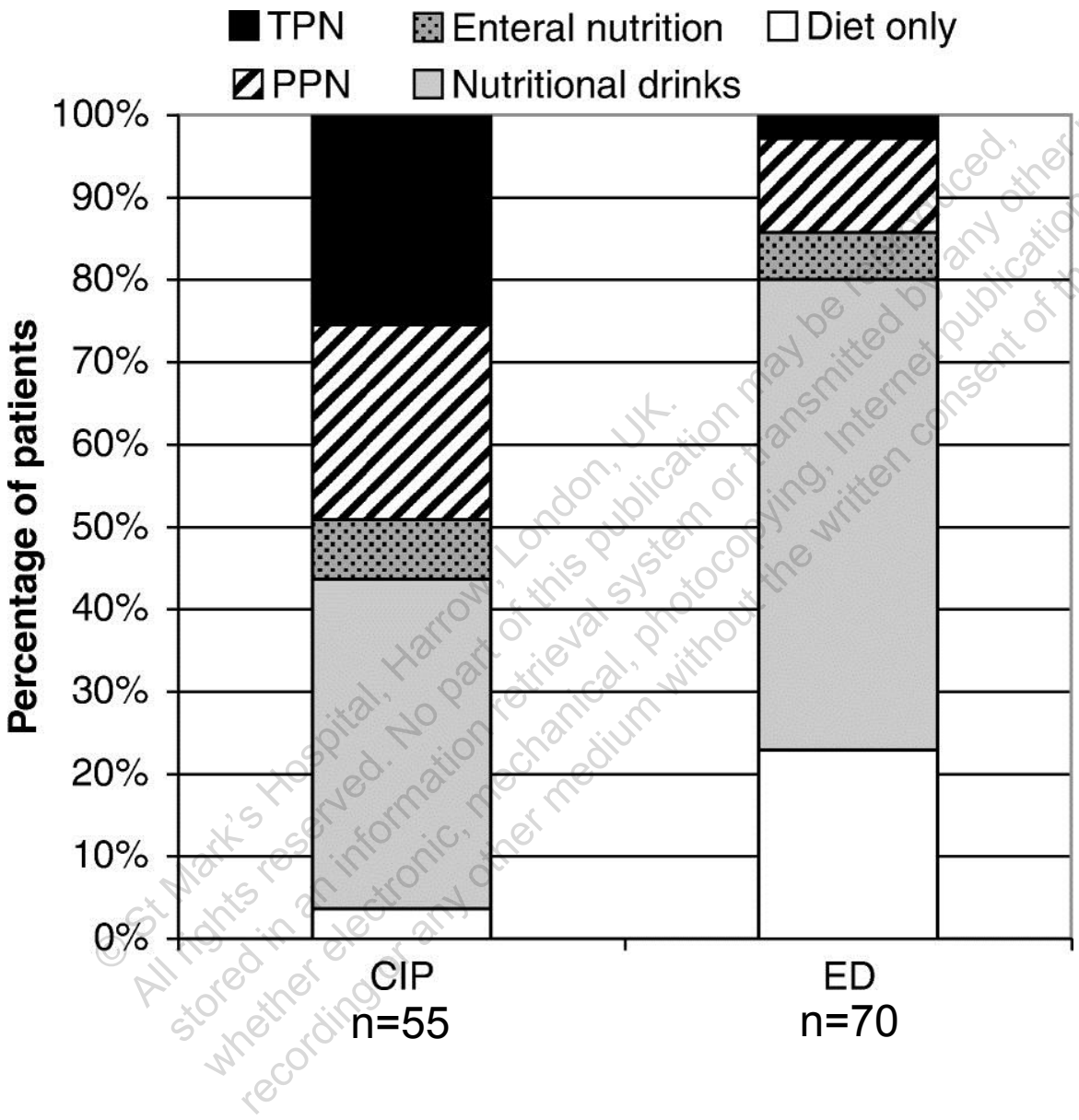
# Relamorelin






Lembo et al 2016 Gastroenterol

# Nutritional management CIPO vs Enteric Dysmotility






Lindberg et al *Scandinavian Journal of Gastroenterology* **2009,** 44, 692-699.

# Enteric dysmotility

A label searching a patient group

Defined by what it is NOT

- neither CIPO nor normal
- yet more than IBS

UNLESS, enteric dysmotility + opioids leads to CIPO

## Miss XX, hair and nail technician
## born 1979, referred 2009

Constipation

- Bowel opening once a week, laxative dependent

Abdominal pain – worse with laxatives

Previously seen

- two gastroenterologists (normal UGI endoscopy, colonoscopy and Ba follow through)
- one general surgeon (normal Ba enema)

“Hard-working…sensible…family-oriented girl”

## Miss XX

Reflux symptoms (omeprazole 40mg bd)

Dental erosions

Food avoidance

Weight 54kg, BMI 21

Only child, parents separated age 11

Lives with mother, no past traumas admitted

Past history of anorexia ("…not an issue now")

# Miss XX

Diagnosis: atypical eating disorder

Referred to Eating Disorder Unit

- Out-patient management plan
- Patient defaulted after 3 months

# Miss XX

2012

- Re-referred (new GP and colo-rectal surgeon)
- Colectomy 2001, now seeking reflux surgery
- BMI 17.8

Patient persuaded to accept diagnosis (mother)

Transferred Eating Disorder Unit

2014 – BMI 23, menstruating, at work

# Eating Disorders in GI Practice

| | Eating Disorder GI | Eating Disorder (Ψ) | Functional Constipation |
|---|---|---|---|
| Mean age | 32 (17-48) | 22 (16-37) | 34 (18-53) |
| Marital status | 90% single | 90% single | 35% single |
| Domicile | 65% parents | 60% parents | 5% parents |
| Employment | 35% fashion | 45% fashion | 0% fashion |
| Age at parental separation | 10 (7-24) | 16 (4-27) | 19 (18-21) |
| Initial BMI | 17 (13-24) | 16 (13-22) | 22 (18-27) |

# Eating Disorders
## Making a Diagnosis

### Conventional

Absolute weight loss
- Self induced (vomit, laxatives)

Distorted body image
- Express “need” to lose weight

Endocrine dysfunction

### GI Practice

GI symptoms at forefront
- Weight loss and vomiting

Persistent denial of intentional weight loss

Resistant to improving nutritional state

Personality disturbance

Endocrine dysfunction

# Prognostic Factors

| | Good outcome (n=10) | Poor outcome* (n=10) |
|---|---|---|
| Parental separation | 4/10 | 10/10 |
| Living with parent | 4/10 | 9/10 |
| Unemployed | 5/10 | 10/10 |
| Time to see psychiatrist | 9 months | 23 months |
| Other psychiatric diagnoses | 5/10 | 10/10 |
| Insight | 6/10 | 0/10 |

*2 deaths

# Eating Disorders in GI Practice

Early recognition

Minimise admissions

Early familial support

Early psychiatric referral

# Mrs XXX, born 1973
# Primary school teacher

2 years abdominal pain, nausea, constipation

BMI 19.7 stable, but “bloated”

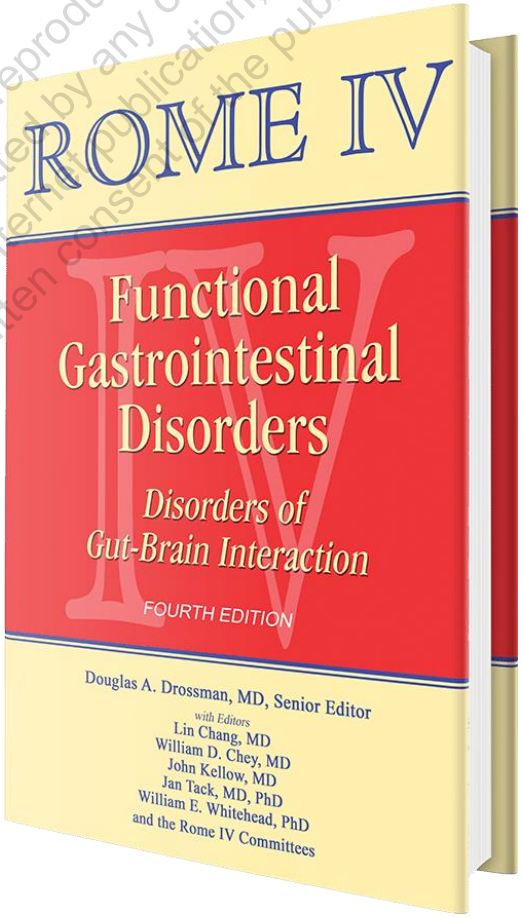
PMH: rotator cuff injury surgically repaired 2 years ago

Occasional smoker (marijuana once a week)

# Isn't this just constipation…with a cause?

C6. Diagnostic Criteria for Opioid-Induced Constipation

1. New, or worsening, symptoms of constipation when initiating, changing, or increasing opioid therapy that must include 2 or more of the following:
   a. Straining during more than one-fourth (25%) of defecations
   b. Lumpy or hard stools (BSFS 1–2) more than one-fourth (25%) of defecations
   c. Sensation of incomplete evacuation more than one-fourth (25%) of defecations
   d. Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations
   e. Manual maneuvers to facilitate more than one-fourth (25%) of defecations (eg, digital evacuation, support of the pelvic floor)
   f. Fewer than three spontaneous bowel movements per week
2. Loose stools are rarely present without the use of laxatives



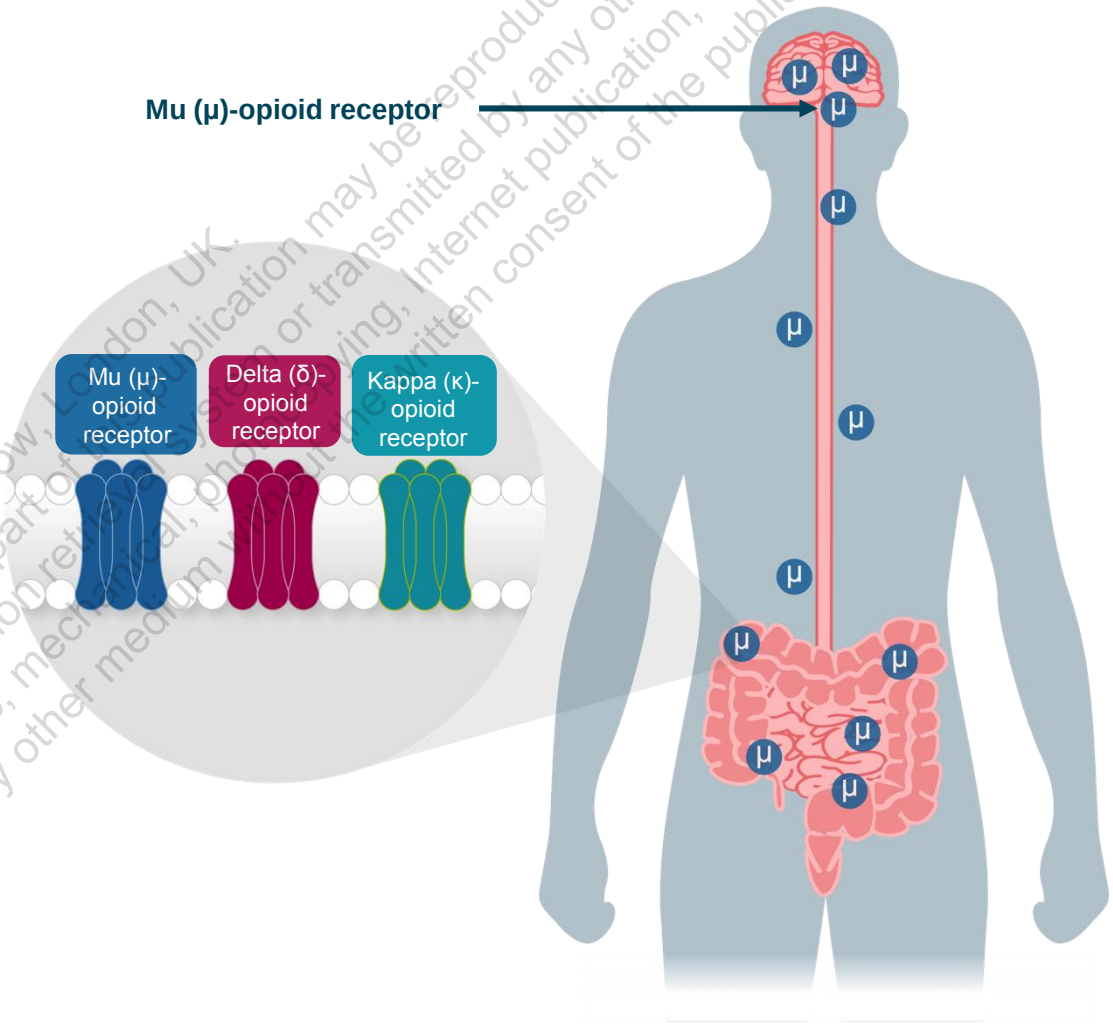



Simren M. *et al. Curr Gastroenterol Rep* 2017;19:15.

# Opioid receptors and the gut

Central opioids inhibit neurosecretion via the sympathetic nervous system, whereas GI opioids inhibit locally.

5-hydroxytryptamine (5-HT) and sodium ($Na^+$) are the terminal transmitters





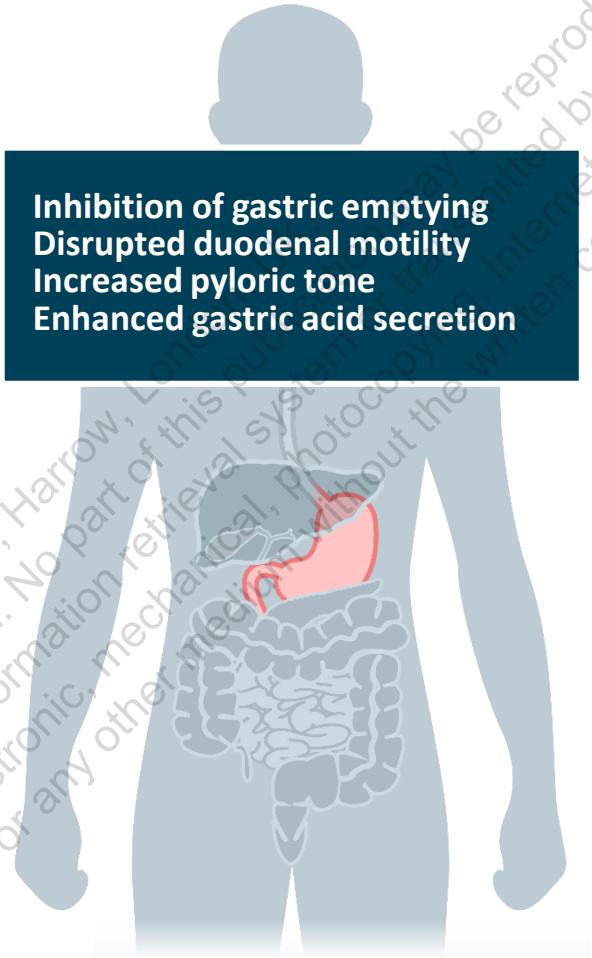

Holzer P. *Requl Pept* 2009;155:11–17.

# Opioid effects on different segments of the GI tract

**Gastroduodenum**

**Inhibition of gastric emptying**
**Disrupted duodenal motility**
**Increased pyloric tone**
**Enhanced gastric acid secretion**

**Anorexia**
**Nausea**
**Gastroesophageal reflux**

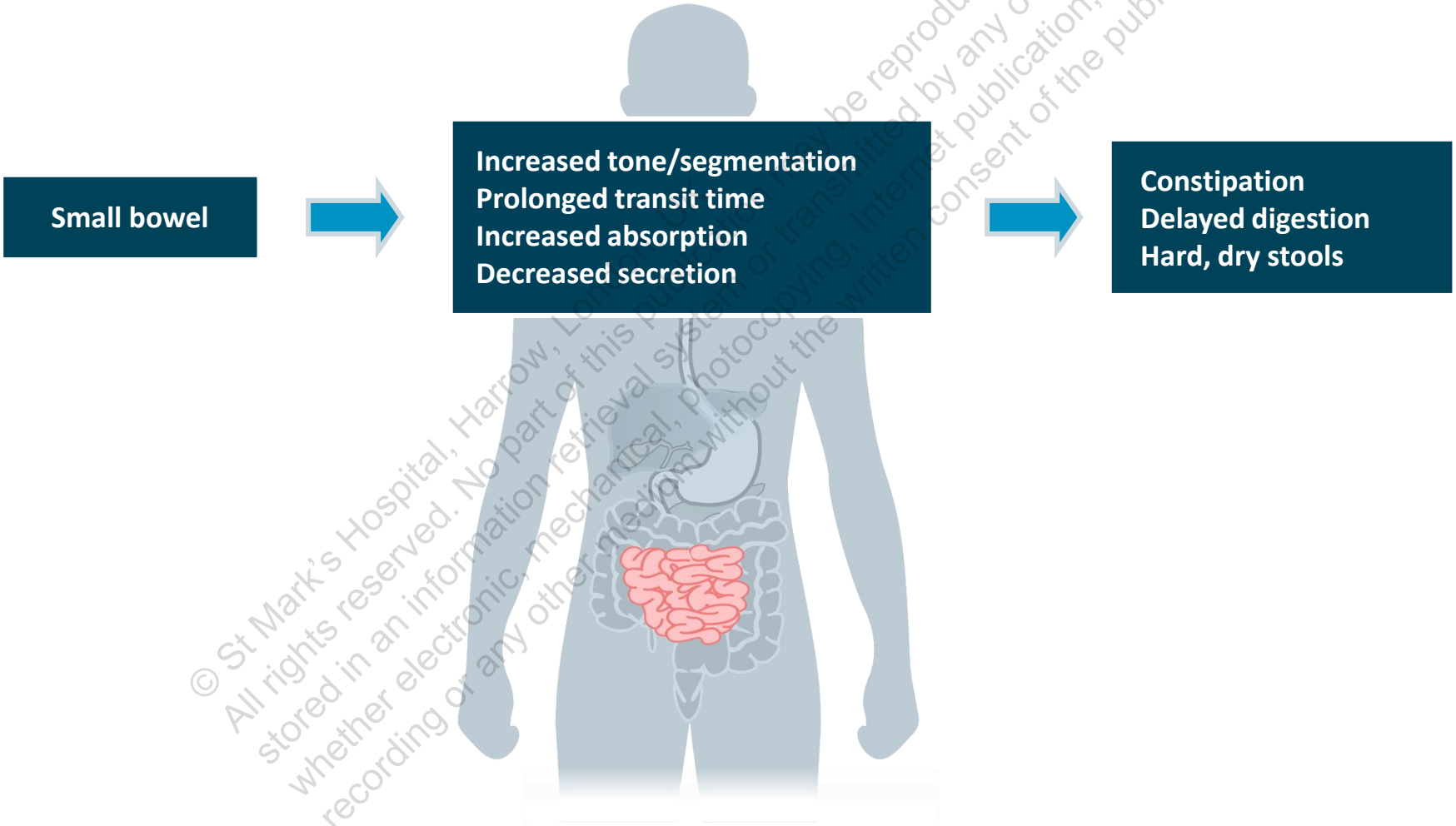




GI, gastrointestinal.

De Schepper HU *et al. Neurogastroenterol Motil* 2004;16:383–94.

# Opioid effects on different segments of the GI tract






GI, gastrointestinal.

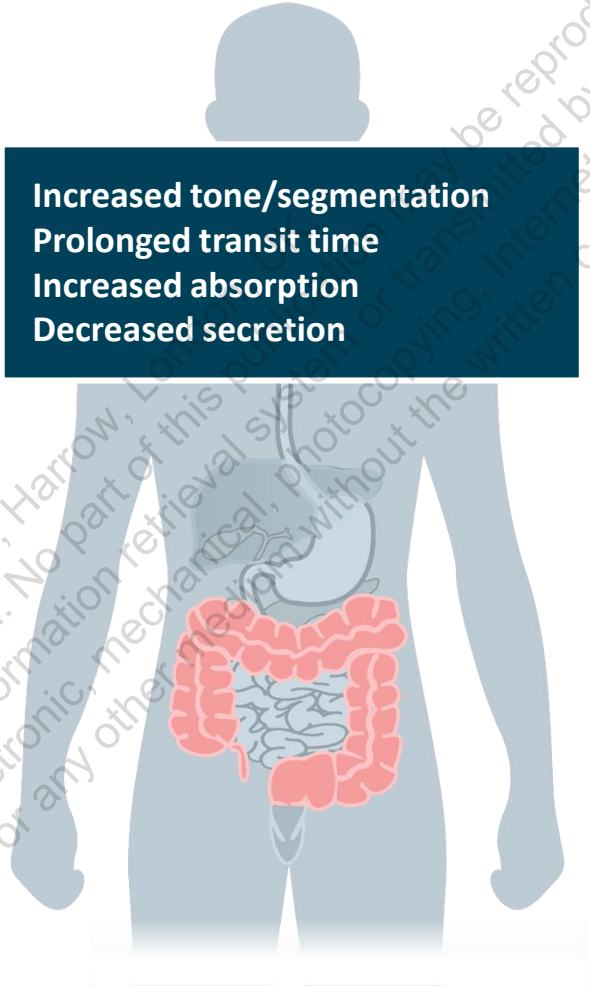
De Schepper HU *et al. Neurogastroenterol Motil* 2004;16:383–94.

# Opioid effects on different segments of the GI tract

**Colon**

**Increased tone/segmentation**
**Prolonged transit time**
**Increased absorption**
**Decreased secretion**

**Constipation**
**Dry, hard stools**
**Bloating and distension**
**Spasm, cramps, pain**

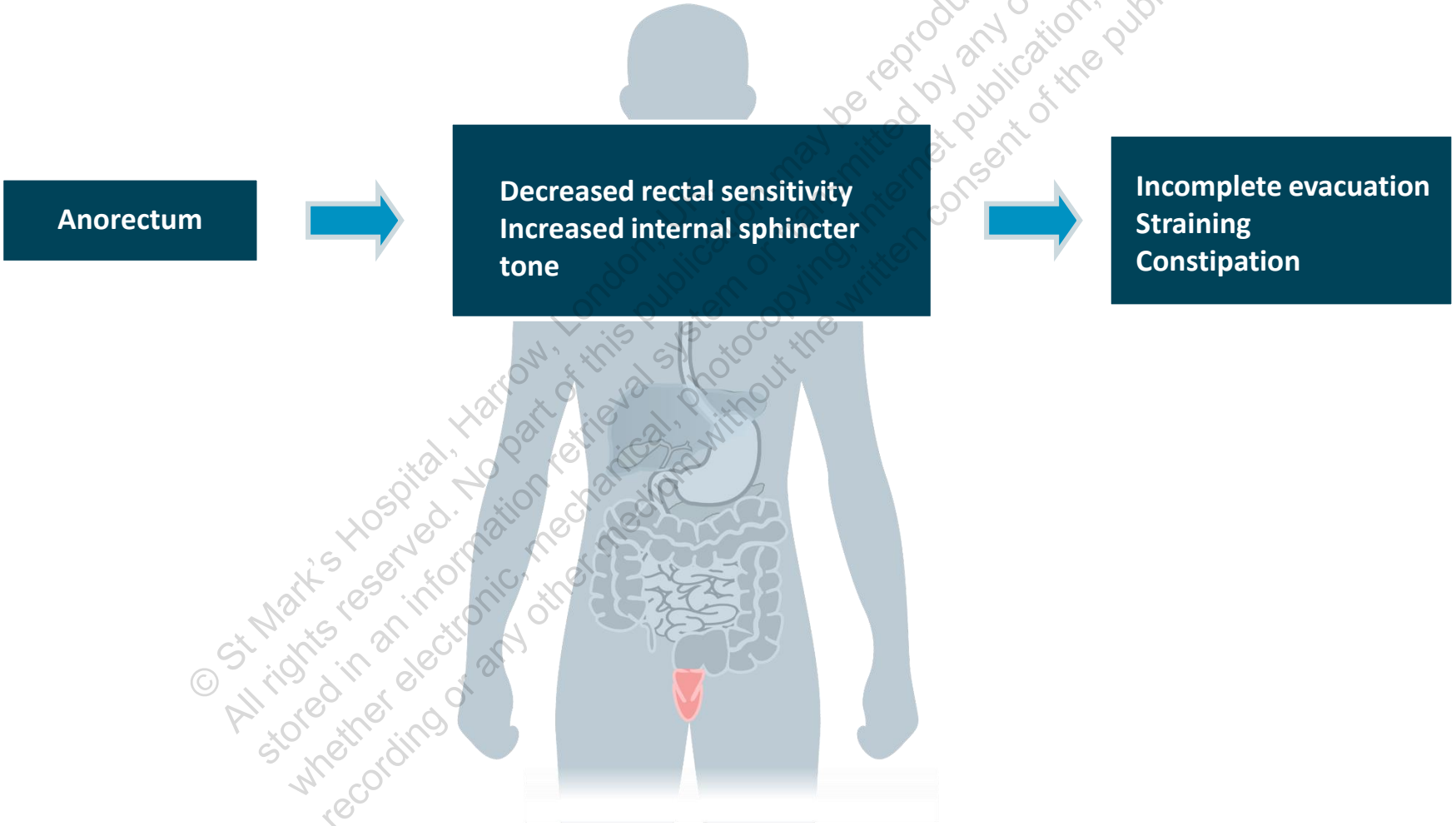




GI, gastrointestinal.

De Schepper HU *et al. Neurogastroenterol Motil* 2004;16:383–94.

# Opioid effects on different segments of the GI tract






GI, gastrointestinal.

De Schepper HU *et al. Neurogastroenterol Motil* 2004;16:383–94.

# Common treatments for constipation

| Common treatments for constipation |
| --- |
| **Bulking agents**<br>– Psyllium<br>– Calcium polycarbophil<br>– Bran<br>– Methylcellulose |
| **Osmotic laxatives**<br>– Lactulose<br>– Polyethylene glycol |
| **Wetting agents**<br>– Dioctyl sulfosuccinate |
| **Stimulant laxatives**<br>– Senna<br>– Bisacodyl |
| **Others**<br>– Prucalopride<br>– Lubiprostone |
| **Biofeedback therapy for dyssynergistic defecation** |
| **Surgery in the treatment of severe colonic inertia** |

None of the laxatives address the underlying opioid receptor mechanism of bowel dysfunction.

Additionally, long-term data is very limited



Remes Troche JM, Rao SSC. *Curr Gastroenterol Report* 2006;8:291–299; Kurz A, Sessler DI. *Drugs* 2003;63:649–671; Sloots *et al. Dig Dis Sci* 2010; 55:2912-2921.

# Do laxatives help?

Pain Medicine

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Article Contents

## Laxatives Do Not Improve Symptoms of Opioid-Induced Constipation: Results of a Patient Survey

Anton Emmanuel, MD; Martin Johnson, MRCGP; Paula McSkimming, BSc (Hons); Sara Dickerson, MSc



| | Total population | Ever used laxatives?* | | Opioid strength† | | Number of laxatives taken‡ | | |
|---|---|---|---|---|---|---|---|---|
| | N=198 | Yes n=134 | No n=50 | Weak only n=116 | Strong only n=42 | 1 n=92 | 2 n=19 | 3 n=9 |
| N (missing) | 185 (13) | 134 (0) | 50.0 (0) | 106 (10) | 39 (3) | 92 (0) | 19 (0) | 9 (0) |
| BFI total score, mean (SD) | 52.0 (31.51) | 58.24 (30.24) | 36.52 (29.0) | 49.83 (31.01) | 51.35 (33.05) | 55.80 (29.50) | 65.3 (32.57) | 85.59 (13.42) |
| BFI total score >28.8, N (%) | 139 (75.1) | 109 (81.3) | 30 (60.0) | 80 (75.5) | 27 (69.2) | 74 (80.4) | 16 (84.2) | 9 (100.0) |

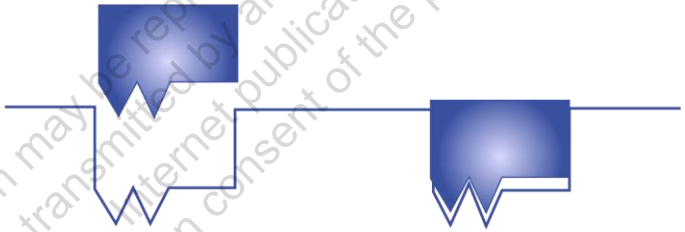
*Excludes 14 patients whose laxative use was unknown; †Excludes 40 patients taking combined strong and weak opioid therapy; ‡Excludes 50 patients taking no laxatives.

Emmanuel A, *et al. Pain Med* 2016; 8. doi: 10.1093/pm/pnw240. [Epub ahead of print]

# Opioid agonists and antagonists
# Peripheral mu-opioid receptor antagonists (PAMORAs)

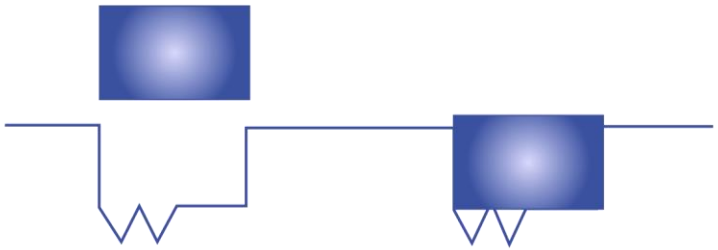
**Agonist:**

- Fits perfectly with the receptor and activates it
- Produces analgesia



**Antagonist:**

- Binds to the receptor, but does not activate it
- Does not produce analgesia
- Used to counteract overdose if active systemically or to improve constipation if given locally





Leppert W. *Drug Des Devel Ther* 2015;16;9:2215−31.

# Naloxegol

The KODIAC-04 and KODIAC-05 studies were identical phase 3 studies that were conducted to assess the safety and efficacy of MOVANTIK compared to placebo in adult patients with chronic non-cancer pain and OIC[1]

## Primary Efficacy Endpoint[1]

**More Bowel Movements**
≥3 SBMs/week and
≥1 SBM/week over baseline

+

**Over a Period of Time**
≥9 of the 12 study weeks and
≥3 of the last 4 weeks

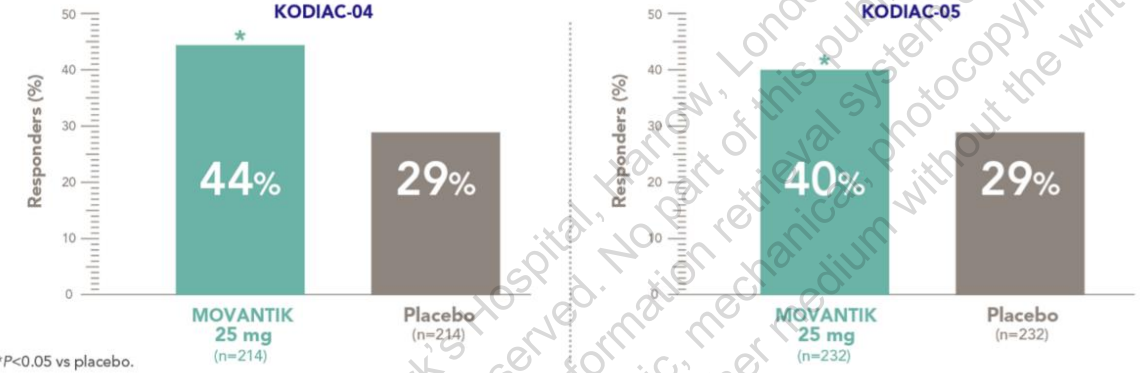
=

**RESPONSE**
(Primary Endpoint)

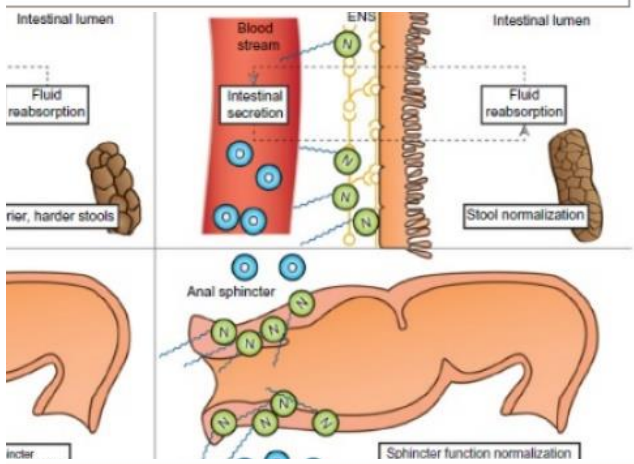
## Secondary Efficacy Endpoints[1,2]

- Response rates in laxative users with OIC symptoms*

Primary endpoint:
Response rate in the overall population[1,2]

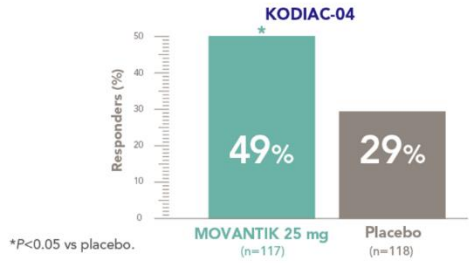



*P<0.05 vs placebo.



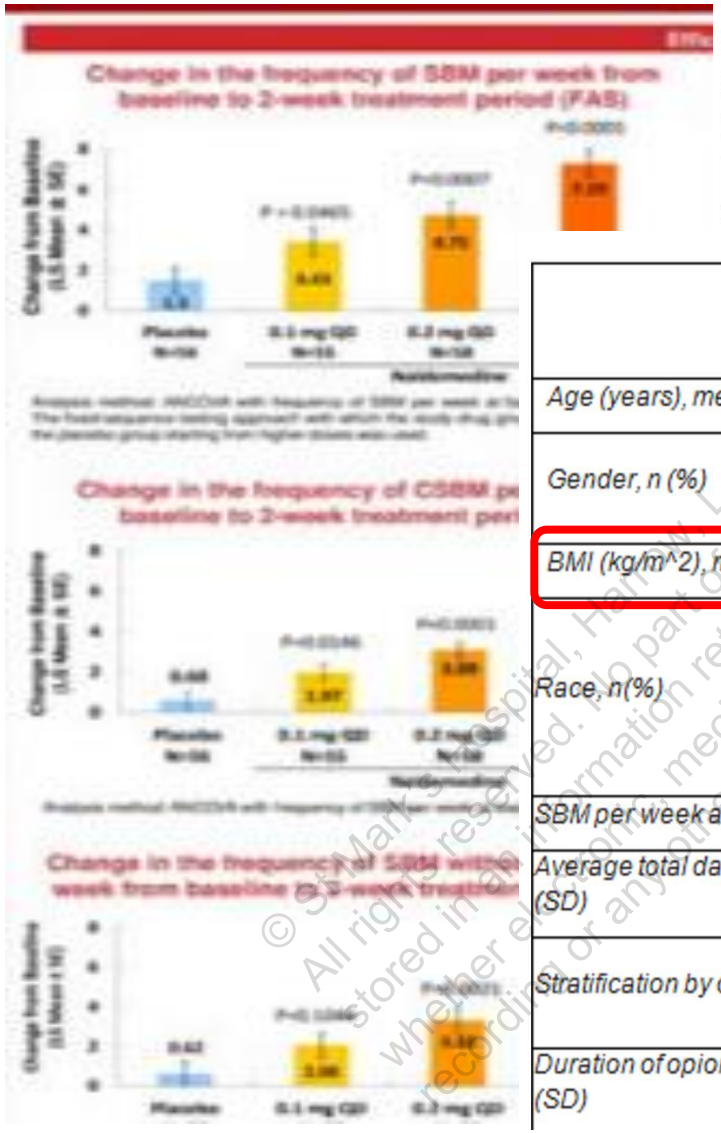


Response rate in laxative users with OIC symptoms[1,2]




*P<0.05 vs placebo.

# Naldemedine



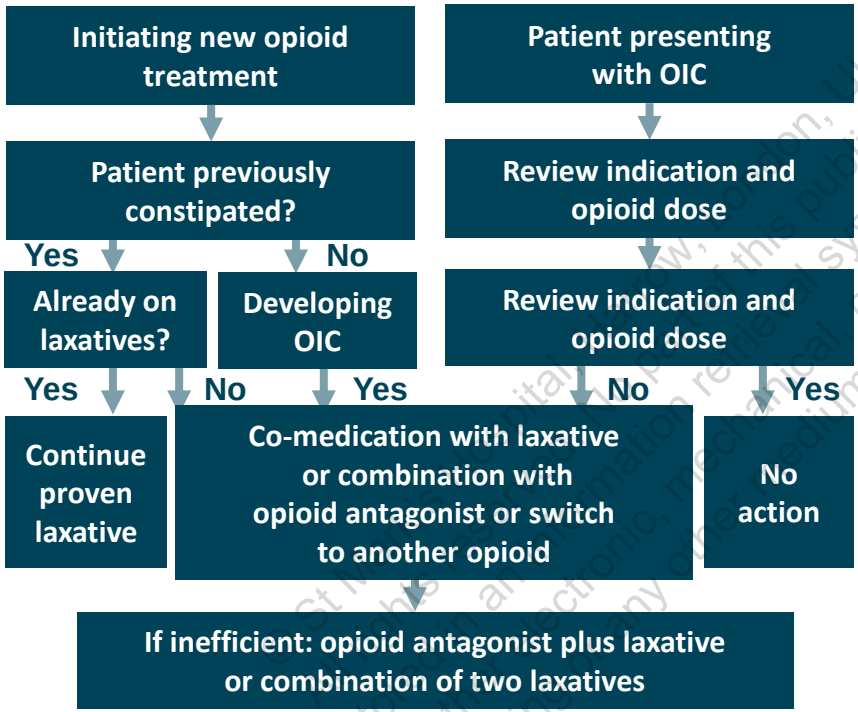


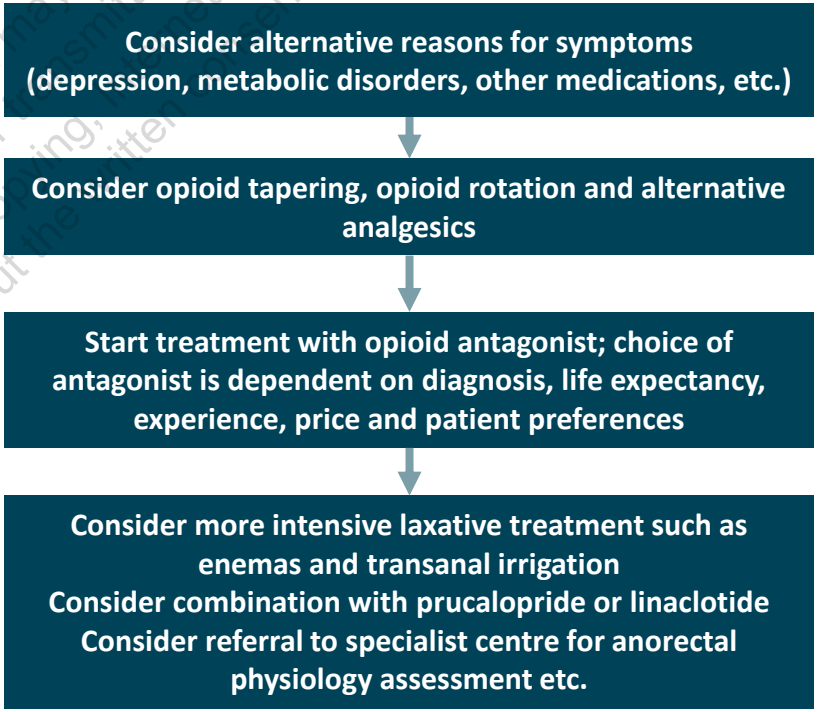

**FDA Approves Symproic® (naldemedine) Once-Daily Tablets C-II for the Treatment of Opioid-Induced**




| | | Naldemedine 0.2 mg N=273 | Placebo N=272 |
|---|---|---|---|
| Age (years), mean (SD) | | 53.3 (10.44) | 53.4 (11.03) |
| Gender, n (%) | Male | 112 (41.0) | 104 (38.2) |
| | Female | 161 (59.0) | 168 (61.8) |
| BMI (kg/m^2), mean (SD) | | 31.35 (7.37) | 31.30 (6.77) |
| Race, n(%) | Caucasian | 216 (79.1) | 220 (80.9) |
| | African American | 53 (19.4) | 48 (17.6) |
| | Other | 4 (1.5) | 4 (1.5) |
| SBM per week at baseline; mean (SD) | | 1.31 (0.746) | 1.30 (0.713) |
| Average total daily dose of opioid at baseline (mg); mean (SD) | | 125.23 (117.953) | 139.66 (153.668) |
| Stratification by opioid dose (mg), n (%) | 30-100 | 155 (56.8) | 153 (56.3) |
| | >100 | 118 (43.2) | 119 (43.8) |
| Duration of opioid use prior to screening (months), mean (SD) | | 61.10 (62.035) | 61.81 (58.336) |

# Opioid-induced constipation and bowel dysfunction: A clinical guidance




OIC, opioid-induced constipation.

Müller-Lissner *et al. Pain* Med 2016; doi: 10.1093/pm/pnw255 [Epub ahead of print]; Drewes AM *et al. Scan J Pain* 2016;11:111–22

# Narcotic Bowel Syndrome

Clinical scenario where opioids sensitise the nerves, exacerbating pain (5-10% opioid users)

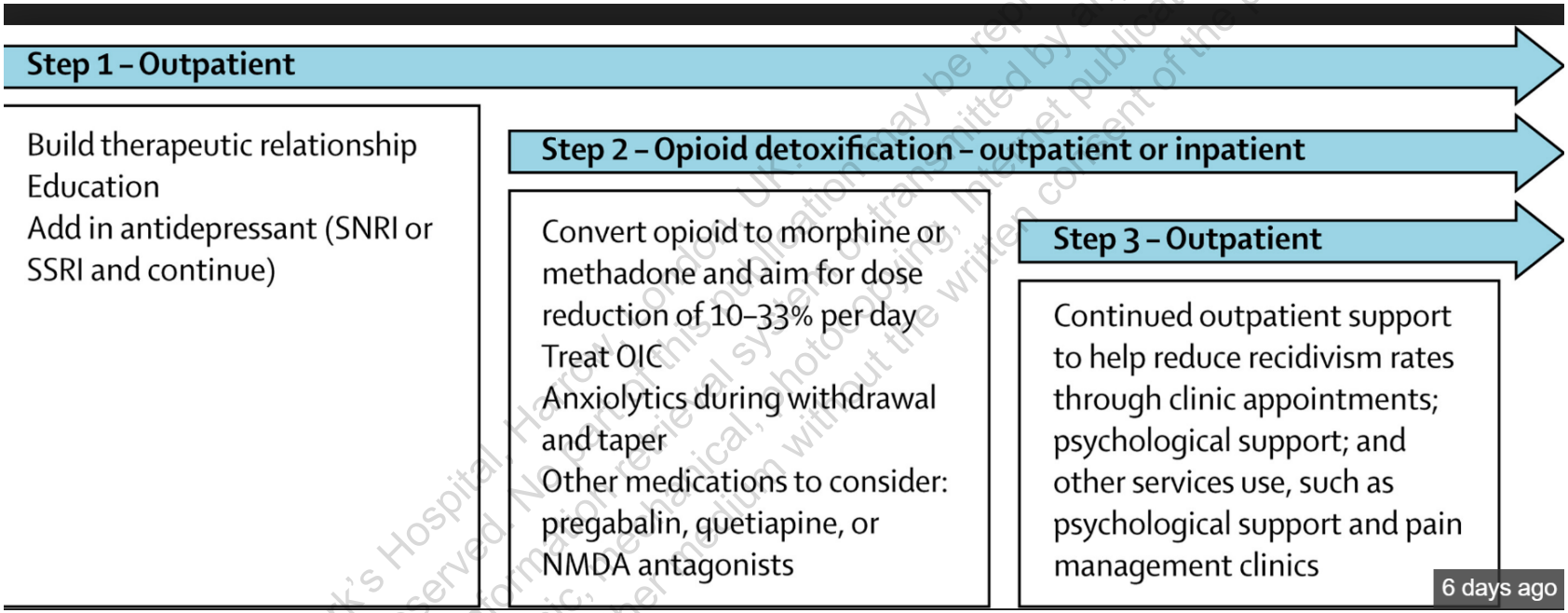
Chronic or frequently recurring abdominal pain that iss treated with acute high-dose or chronic narcotics

The nature and intensity of the pain is not explained by a current or previous GI diagnosis

Two or more of the following:

- The pain worsens or incompletely resolves with continued or escalating dosages of narcotics
- There is marked worsening of pain when the narcotic dose wanes and improvement when narcotics are re-instituted (soar and crash)
- There is a progression of the frequency, duration, and intensity of pain episodes

# Narcotic Bowel Syndrome




In patient weaning with:

Benzodiazepine, Clonidine, Psychotherapy – CAREFUL